NEUROBIOLOGY OF AFFECTIVE DISORDERS:

where do we stand?

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In Search of the Holy Grail:

- Neurobiology of affective disorders began with serendipity findings and “ex juvantibus” criteria
- Base research couldn’t keep the pace with clinical data and applied research
- Nowadays a huge amount of studies with controversial data and not replicated findings
- Many hypothesis but no conclusions

First Steps: Serendipity

Reserpine (hypertension) → depression

IMAO (tuberculosis) → euphoria

Biogenic amine hypothesis (5HT, NA, DA)

Further observations involved more and more systems (Ach, Gaba, Endorphin system, Glut. etc. etc. etc. etc…)

.. leading to an amine Imbalance framework (increased in mania/ decreased in depression)

In Search of the Holy Grail:

"…Affective state is a neurobiological balance, but there is no consistent body of evidence to date to confirm that the two poles of the illness (mania and depression) are biological opposites of each other…"

*(*Fatemi & Clayton in "Medical Basis of Psychiatry" Humana Press 2008*)*

In Search of the Holy Grail:

"…Many studies indicate abnormalities and variability in biochemical, neuroendocrine and second messenger system function, but they do not shed bright light on a specific neurobiology of affective illness either mania or depression …"

"…The central defect is yet to be identified… "

*(*Fatemi & Clayton in "Medical Basis of Psychiatry" Humana Press 2008*)*

A Milestone in the search of the Holy Grail

"…the fact that no single gene, pathway, or brain abnormality is likely to ever account for the condition is an extremely important first step in order to try to collect most recent findings into an integrated perspective …"

(Maletic V, Raison C. "Integrated neurobiology of bipolar disorder" Front Psychiatry. 2014 Aug 25;5:98)

In Search of the Holy Grail:

- We are very far from being able to transfer research data into clinical practice
- What follows is a summary of the most promising findings in neurobiology of affective disorders
- These observations may help to make progresses in research and to stimulate clinicians in their everyday work

Monoaminergic Hypothesis and Beyond

Beyond Monoaminergic Hypothesis:

Classic monoaminergic hypothesis and hypothalamic–pituitary–adrenal (HPA) axis hyperactivity have guided research efforts in the field for decades, but they have not generated any conclusive model either for the pathophysiology of depression or for antidepressant drugs' action

(Ferrari F, Villa RF. 2017)

Beyond Monoaminergic Hypothesis:

In its original form the monoamine hypothesis is clearly inadequate, as it does not provide a complete explanation for the actions of antidepressants and the pathophysiology of depression.
It has evolved over the years to include, for example, adaptive changes in receptors…

(Hirschfeld RM History and evolution of the monoamine hypothesis of depression.J Clin Psychiatry. 2000;61 Suppl 6:4-6.)

Beyond Monoaminergic Hypothesis:

…still, it does not address key issues such as why antidepressants are also effective in other disorders (panic, obsessive-compulsive, bulimia), or why all drugs that enhance serotonergic or noradrenergic transmission are not necessarily effective in depression

(Hirschfeld RM History and evolution of the monoamine hypothesis of depression.J Clin Psychiatry. 2000;61 Suppl 6:4-6.)

Beyond Monoaminergic Hypothesis:

It is becoming evident that depression is not related only to monoamines but to other pathogenetic factors. Other emerging theories should integrate monoaminergic hypothesis

(Maletic V, Raison C. "Integrated neurobiology of bipolar disorder" Front Psychiatry. 2014 Aug 25;5:98)

Hypothalamic-Pituitary-Adrenal Axis Dysfunction

Hypothalamic-Pituitary-Adrenal Dysfunction

Stress is perceived by the brain and transmitted to the hypothalamus leading to the HPA activation. HPA activity is regulated by adrenocorticotropic hormone-releasing factor (corticotropin-releasing factor (CRF) and vasopressin (AVP) secreted from the hypothalamus, which in turn stimulates the pituitary to secret the adrenocorticotropic hormone (ACTH) that finally activates the secretion of glucocorticoids (cortisol in humans) from the adrenal cortex. Glucocorticoids then bind to their receptors within the HPA axis where they exert a feedback on CRF, AVP and ACTH secretion

(Villa RF, Ferrari F, Gorini A (2012)

Hypothalamic-Pituitary-Adrenal Dysfunction

Glucocorticoids not only control peripheral functions like metabolism and immunity but have also several central effects:

- regulate neuronal survival,
- neurogenesis,
- sizes of hippocampus,
- formation of new memories
- emotional assessment of event

Therefore they are a key link between stress and brain functioning

(Villa RF, Ferrari F, Gorini A (2012)

Hypothalamic-Pituitary-Adrenal Dysfunction

Several studies observed an increased activity of the HPA axis in depressed patients:

- increased levels of cortisol in saliva, plasma and urine
- increased level of CRF in limbic brain
- increased size (as well as activity) of the pituitary and adrenal glands

But only some subgroups of depressed patients show HPA axis activation, suggesting that only a specific genetic predisposition/adverse events interaction would lead to vulnerable phenotypes with amplified stress reactivity

(Kendler KS, Gardner CO, Prescott CA (2006)

Hypothalamic-Pituitary-Adrenal Dysfunction

Patients with Bipolar Disorder are also supposed to have a hyperactive HPA axis, high levels of systemic cortisol, and non-suppression of its circulating levels in the dexamethasone suppression test.
Mechanisms of HPA axis dysregulation are incompletely known at present, as is its role in the risk of the disease in vulnerable subjects.

(Ising M, Lauer CJ, Holsboer F, Modell S. 2005)

Hypothalamic-Pituitary-Adrenal Dysfunction

Main problem with this model:

Assessment of dexamethasone-suppression-CRH test in high-risk individuals who developed an affective disorder in a 10-year follow-up period revealed no premorbid differences in their cortisol response compared to healthy controls

(Ising M, Lauer CJ, Holsboer F, Modell S. The Munich vulnerability study on affective disorders: premorbid neuroendocrine profile of affected high-risk probands. J Psychiatr Res. 2005;39(1):21–8)

Role of Immune - Inflammatory Imbalance in Depressive Disorder

Inflammation in MD, First Findings:

Early papers about inflammation and monocytic and T cell activation in depression were firstly published in 1990s

More recently depressed patients have been shown to exhibit evidence of inflammation, as manifested by increased concentrations in peripheral blood and CSF of inflammatory cytokines like tumour necrosis factor- alpha (TNF-α), interleukin IL-1 and IL-6

(Dowlati Y, et al 2010)

Cytokines Effects and Depression:

Administration of cytokines [e.g. interferon-alpha (IFN-α)] and of cytokine inducers (lipopolysaccharide and typhoid vaccination) led to behavioural symptoms similar to those of depressed patients. (Miller AH, Maletic V, Raison CL (2009)

Cytokines may influence both metabolism of NA, 5-HT, DA and neuroendocrine functions (flattening cortisol curve and increasing cortisol concentrations), suggesting a link between Inflammatory process activation and HPA axis.

(Irwin MR, Miller AH (2007) Iwata M, Ota KT, Duman RS (2013) Miller AH (2010)

T Cells and Depression:

- Early results confirmed through meta-analytic approaches reached the consensus that statistically reliable decreased T cell responses exist in both stressed and depressed individuals

- T cells of depressed PTS may undergo increased apoptosis

- Nevertheless, mechanisms of T cell alterations have yet to be completely established

(Irwin MR, Miller AH (2007)
(Sephton SE, et al 2009)

Oligodendroglia, Gaba and Depression:

Reduction in numbers/density of oligodendrocytes and structural/functional GABAergic interneurons changes related to inflammatory insults are one of the most prominent findings in depression

Although postmortem data suggest neuroimmune etiology in a subgroup of depressed individuals, some authors do not believe that all depression-associated abnormalities are reflective of a neuroinflammatory process or even that all immunological activity in the brain is deleterious

(Mechawar N, Savitz J. 2016)

Immune/Inflammatory Imbalance in Bipolar Disorder

Cytokines and Inflammatory state in BD:

- Major episodes of either polarity result in an inflammatory response shown in several studies
- Increased levels of pro-inflammatory cytokines (IL-1, IL-6 and TNF) and C-reactive protein in peripheral blood has been found
- Resolution of acute episodes has been shown to normalize some PIC like IL-6 but not TNF
- Whereas a chronic low-level inflammatory state seem to persist even in euthymic patients

(Ising M et al 2005)

Specific Role of IL6 in Bipolar Disorder:

- IL 6 is a ubiquitous inflammatory cytokine with different actions: from repair of cellular elements to augmenting the response to injury in various types of tissue damage

- Many neural cells are the target of IL-6 trans-signaling and modulation of its activity may have important effects in neuropsychiatric disorders

- Several studies show an increase in peripheral circulating levels during acute mood episodes of either polarity

(Agorastos A, et al 2014 ; Munkholm K, et al 2015 ; Muneer A. 2016)

Interconnection HPA, Amines, Cytochines:

- Episodes in BD activates the HPA axis (increased cortisol/stimulation of the sympatho-adrenal medullary axis/increased epinephrine and norepinephrine)

- Immune cells (monocytes, macrophages, T-cells) secrete cytochines that trigger microglia, causing inflammation and further activating the HPA axis

- Stress hormones lead to constant low-grade inflammation that stimulate the progression of the bipolar diathesis (Ising M, Lauer CJ, Holsboer F, Modell S. 2005)

Neurotrophic Factors

Neurotrophins and Brain Morphology:

Neuroimaging and post mortem morphometric studies in depressed patients found structural alterations across various regions:

- Volume reduction in prefrontal cortex
- Volume reduction in cingulate cortex,
- Hippocampal atrophy
- Decreased glial in cortical and limbic brain

(Smith MA, Makino S, Kvetnansky R, Post RM (1995)

Neurotrophins and Brain Morphology:

Neurotrophic factors like BDNF, nerve growth factor (NGF) and neurotrophin-3 exert their actions in the adult brain, where their expression is regulated by stress and psychotropics

BDNF expression is downregulated by stress in dentate gyrus, where it may contribute to the atrophy

In contrast to the effects of stress Antidepressants increase the expression of BDNF both in hippocampus and in frontal cortex

(Duman RS (2002)

Neurotrophins and Affective Disorders:

- BDNF plasma levels are reduced to the same extent in manic and depressive episodes
- They are not significantly altered in euthymia
- They recover with treatment of acute episodes of both polarity
- BDNF plasma levels may be a potential biomarker of mood states, disease activity and disease progression for BD

(Polyakova M et al 2015 ; Fernandes BS 2015. ; Fernandes BS 2011)

Neurotrophins and Monoamines:

Studies suggest that BDNF is the link among stress, and hippocampal atrophy in depression

BDNF is up-regulated by the transcription factor CREB, whose expression is stimulated by antidepressant treatments that increase NA and/or 5-HT in the synaptic cleft

Therefore, BDNF is also tightly linked to the monoaminergic hypothesis of depression

(Duman RS (2002) Siuciak JA et al 1996)

Ketamine, Glutamate and Neuroplasticity

Ketamine in depressive disorder:

A meta-analysis revealed that response rate of single dose ketamine after 24h is about 52.6%, this efficacy would last about 3 days decreasing gradually up to a 10.9% of response rate remained at two weeks. Repeated ketamine injection have a higher response rate (70.8%), and the efficacy lasts about 18 days on average

(Newport et al., 2015 Murrough et al., 2013)

Ketamine in depressive disorder:

The significant difference in time of onset between ketamine and other AD is of special clinical significance

The possible mechanism of ketamine AD effect has been described in several reviews stating that the blockade of NMDA receptor and potentiation of AMPA receptor is of key significance in ketamine's efficacy

(Browne and Lucki, 2013; Zunszain et al., 2013; Kavalali and Monteggia, 2015; Scheuing et al., 2015)

Ketamine in depressive disorder:

NMDA and AMPA are two glutamate receptors distributed widely in the brain. Their physiological ligand, glutamate, is the only excitatory neurotransmitter and innervates the majority of neurons in the brain; being the primary neurotransmitter of 80% neocortex neurons and 85% neocortex synapses

(Douglas and Martin, 2007)

Ketamine in depressive disorder:

Brain is largely a “glutamatergic excitatory machine” and all brain functions, particularly cognition and emotion are “ultimately mediated by the changes in excitatory transmission (glutamate) and its counterbalance of the inhibitory component (GABA)”

(Sanacora et al., 2012)

Ketamine in depressive disorder:

Release of glutamate may induce rapid LTP and promote synaptogenesis.
Blocking NMDA receptor and activating AMPA receptor may promote the expression of BDNF gene and promote neuroplasticity synergistically.
Thus glutamate is the primary system regulating neuroplasticity in the brain.

(Sanacora et al., 2012)

The role of Glutamate in affective disorders

Increased levels of glutamate plus glutamine signal in frontal lobes, basal ganglia, left dorsolateral prefrontal cortex and global grey matter of drug-free BIP patients
lower Glx values in the frontal lobes of its with MDD respect to healthy controls
Thus, a hyperglutamatergic state in bipolar disorder is probable, while a hypoglutamatergic state in MDD is more likely

(Dager SR, Friedman SD, Parow A, Demopulos C, Stoll AL, Lyoo IK, et al. (2004) Brain metabolic alterations in medication-free patients with bipolar disorder. Arch Gen Psychiatry 61:450–458)

Ketamine in depressive disorder:

The fast onset of antidepressant efficacy of ketamine may be explained by the following two reasons: (1) ketamine acts directly on NMDA receptor and indirectly on AMPA receptor, while SSRIs mainly act on SERT and indirectly regulate efficacy of glutamate receptors

(Liu B, Liu J, Wang M, Zhang Y, Li L. From Serotonin to Neuroplasticity: Evolvement of Theories for Major Depressive Disorder.Front Cell Neurosci. 2017 Sep 28;11:305)

Open Discussion:

Topics for an open discussion:

What can we state nowadays about neurobiology of affective disorders

How to improve research about neurobiology of affective disorders

How to translate research data into everyday clinical practice with affective disorders

The Role of Oxidative Damage

CNS vulnerability to oxidative stress:

- Highest oxygen consumption of all the organs
- Greater formation of reactive/oxygen/species (ROS) in mitochondrial energy metabolism
- Very high lipids content (substrate for the ROS)
- Neurotransmitters (dopamine) high redox potential
- defenses against free radicals relatively inefficient
- high content of ions (iron/copper) involved in redox

(Morris G, Berk M. 2015)

Oxidative Stress: definition and role

Oxidative stress can be considered as an imbalance between antioxidants and pro-oxidants (with a tilt toward the latter) with the result of a disproportionate formation of free radicals.

At low physiological concentrations, free radicals perform important functions in the central nervous system such as regulation of the destiny of neurons either through growth or programmed cell death.

(Muneer A. 2016)

Oxidative Stress, Glutamate and Cortisol:

Free radical actions may have a key function in fine-tuning the responses of neuronal cells to adverse events, either by promoting resiliency through stress-induced molecular cascades or by getting rid of the severely impaired cells by apoptosis.

Some oxidative stress products cause glutamate excitotoxicity and they have been shown to induce cortisol resistance

(Muneer A. 2016)

Oxidative Stress, Gaba and Glutamate:

In case of persistent severe life stress, the neurologic impact of excessive ROS generation gives rise to continued excitatory, glutamatergic transmission leading to changes suggestive of alterations seen in psychotic disorders.
These include down-regulation of the NMDA receptors, failure of the inhibitory trait of GABAergic interneurons, and reduction of hippocampal volume

(Schiavone S, Jaquet V, Trabace L, Krause KH. 2013)

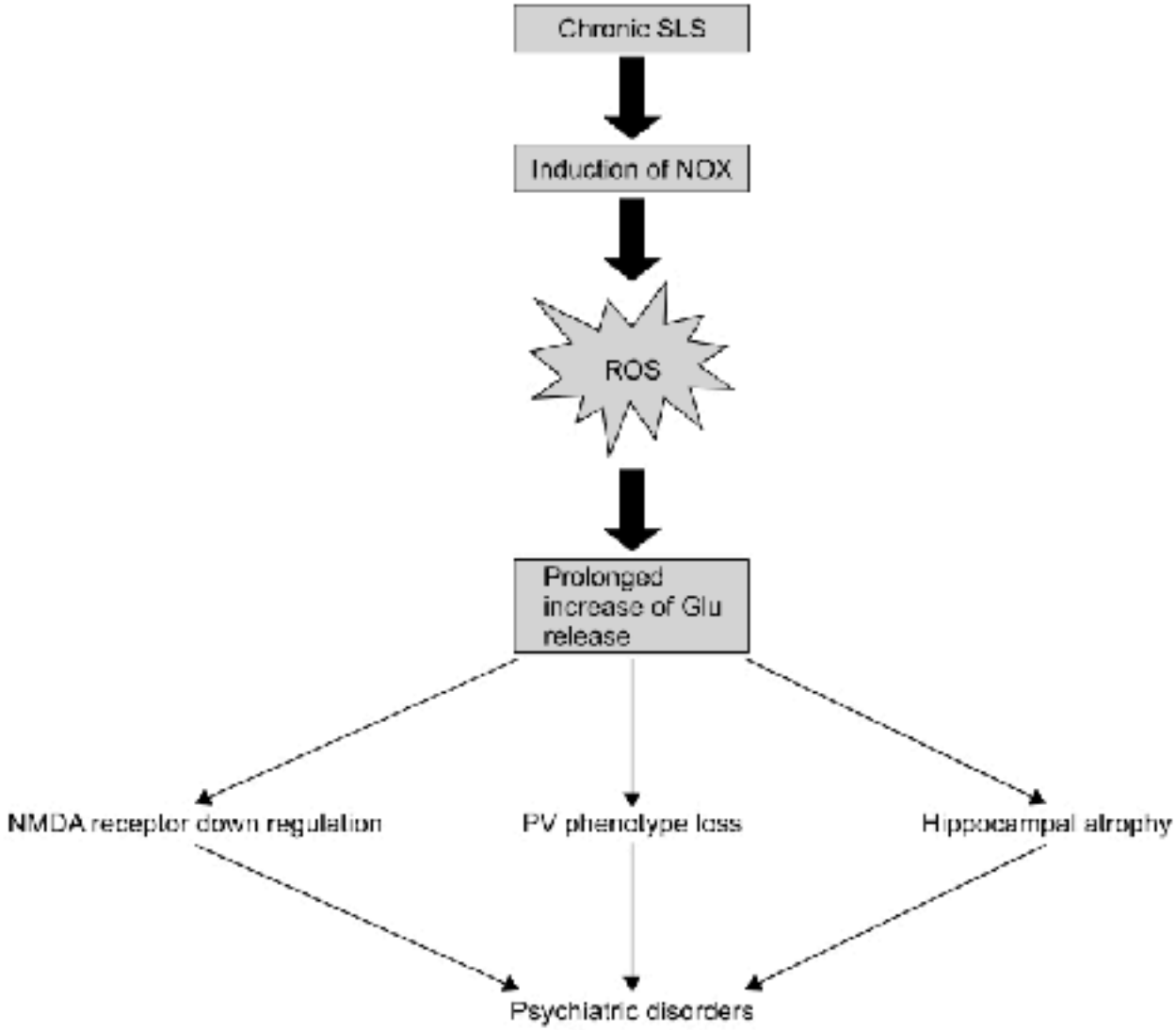
Glutamate excito-toxicity in affective disorders:

In circumstances of stress enhanced brain glutamate may lead to cell damage. Glutamate extracellular concentration can increase up to 100-fold, overwhelming all mechanisms of glutamate reprocessing. Such pathologically increased levels result in atrophic changes in key mood-regulating areas like the hippocampus and amygdala

(Savitz J, et al. 2015)

Oxidative Stress:

Neurobiology of Bipolar Disorder



Neuroplasticity and Depression, an interpretation framework

Neuroplasticity model of depression:

Neuroplasticity includes both morphological and functional adaptation to environment signals, being a complex and not yet fully understood process in brain's adaptation to stress.

Maladaptive neuroplasticity may underlie various psychiatric disorders, such as depression

(Liu B, Liu J, Wang M, Zhang Y, Li L. 2017)

Neuroplasticity model of depression:

Evidence from three domains:

(1) decreased neuroplasticity in hippocampus and pre-frontal-cortex in MD pts

(2) decreased concentration of neurotrophic factors, such (BDNF), in MD

(3) antidepressants would elevate neurotrophic factors and improve neuroplasticity in hippocampus and PFC.

(Serafini, 2012)

Neuroplasticity, Stress and Depression:

Cortisol elevation during chronic stress would exert neurotoxic effect on hippocampus which would result in decreased neurogenesis, synaptogenesis and increased apoptosis of neurons

Vicious circle between dysregulation of HPA axis and morphological/functional deficits of hippocampus may be a key route between stress and depression

(Holsboer and Barden, 1996; Holsboer, 2000; de Kloet et al., 2005)

Neuroplasticity, Stress and Depression:

Vicious Cycle:
morphological loss of neurons further leads to functional deficits loss of long-term potentiation (LTP) or long-term depression (LTD) of hippocampus, which gives rise to decreased GABAergic control of the HPA axis, and the the disinhibition of HPA axis would inversely exacerbate the morphological and functional loss of hippocampus

Biochemical changes and Neuroplasticity:

Chronic stress would induce increased release of glutamate in the hippocampus and prefrontal cortex and blunted neurotransmission of 5-HT and DA in mesocortical circuits.

Particularly high glutamate levels would exert stress related neurotoxic effect on the PFC and hippocampus

(Sanacora et al., 2012 ; Mahar et al., 2014 ; Pizzagalli, 2014)

Biochemical changes and Neuroplasticity:

These neurochemical changes would result in negative influence on neuroplasticity through blunted neurogenesis, disrupted synaptogenesis, diminished dendritic spines and reduced synaptic connections.
Besides, stress would diminish proliferation and promote apoptosis of glial cells, which are responsible for glutamate clearance in the brain

(Rial et al., 2015)

Antidepressants and Neuroplasticity:

AD improve neuroplasticity through:

- monoamine neurotransmitters' stimulation
- increased gene expression of NGF proteins such as BDNF
- reducing release of glutamate, especially in PFC (decreased neurotoxicity and strengthened neurogenesis)
- trough long term potentiation resulting in potentiating synaptogenesis and connectivity

(Du et al., 2006)

Summary:
An Integrated Approach

An Integrated Approach to diagnosis:

From a neurobiological perspective there is no such thing as bipolar disorder.
Rather .. many somewhat similar, but subtly different, pathological conditions produce a disease state that we currently diagnose as bipolarity.
This heterogeneity is reflected in the lack of synergy between our current diagnostic schema and our scientific understanding of the condition

(Maletic V, Raison C. "Integrated neurobiology of bipolar disorder" Front Psychiatry. 2014 Aug 25;5:98)

An Integrated Approach for Research:

Prospective long-term follow-up studies using multimodal (i.e., combination of imaging, cognitive, neurochemical, and genetic assessment) and standardized techniques in well-defined at-risk populations, are needed for better understanding of the neurobiology of affective disorders

(Yatham LN, Torres IJ, Malhi GS, Frangou S, Glahn DC, Bearden CE, et al. The International Society for Bipolar Disorders-Battery for Assessment of Neurocognition (ISBD-BANC). Bipolar Disord. 2010;12(4):351–63)

An Integrated Model for Methodology:

Conceptualized as a multi systemic progressive condition, affective disorders seem to be the expression of a multiple dysregulation of different biological abnormalities that act in concert

Dropping the search for a unique defect and therefore starting to investigate multiple dysfunction in an integrated perspective is probably the very first significant step “in search of the holy grail”.