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Ethiopathogenesis of Depressive Disorders

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Abstract: Etiology of depressive disorders is still unknown. Several factors are involved in its pathophysiology such as neurotransmitters and neuroendocrine alterations, genetics, life events and their appraisal. Some of these components are strictly linked. Subjects with a family member affected by mood disorders are more prone to suffer from depressive disorders. It is also true that receiving feedbacks of indifference or neglect during childhood from one parent who suffer from depression may represent a factor of vulnerability. Indeed, reaction to a specific negative event may determine an increased allostasis which lead to a depressive episode. Thus, a psychological cause does not exclude a neurobiological cascade. Whereas in other cases recurrent depressive episodes appear in absence of any negative life event. This review provides a set of data regarding the current etiopathogenesis models of depression, with a particular attention to the neurobiological correlates and vulnerability factors.

Keywords: Genetics, neurobiology, temperament, unipolar depression, vulnerability.

DEPRESSION-PRONE PERSONALITY AS A VULNERABILITY FACTOR FOR DEPRESSION

In this paragraph we try to elucidate the association between Major Depressive Disorder (MDD) and personality types or character predisposition. First of all we have to point out that most cases of MDD start with high degrees of suffering, in absence of a personality predisposition. This is not just the case of Mood Disorders due to a Medical Condition, or a Depressive Episode in a patient affect by a Bipolar Disorder. We here refer to subjects affected by MDD that share no elements for such a personality predisposition. These patients are said to be affected by endogenous depression. The ancient Greek philosophers studied the melancholic attitudes of humans. Besides several pre-scientific observations, some of them (Rhufus, Teofrastus, Aristotle, Galen) described a variety of mood disorder manifestations [1]. They also tried to find a biological explanation and associate certain personality types to depression. More recently Tellenbach delineated a personality type prone to depression that share many features with the description of several DSM-IV Personality Disorders including Avoidant, Dependent, and Obsessive-Compulsive Personality Disorders [2]. The key for understanding the association between MDD and personality is the concept of vulnerability. Meaning that, because of the subject's scarce coping resources several stressful live events, generally well coped by most of the population, have a chance of becoming *depressogenic*. Somebody might suggest the opposite, that these subjects look at life events with a depressive perception. According to the cognitive theory of depression, cognitive organization, core beliefs and self perception are all factors of vulnerability, albeit it is important to distinguish depressive organization from a depressive episode. Subjects with a depressive organization may never experience a depressive episode. On the other hand, these subjects are more prone to manifest their psychological suffering with a depressive episode. Therefore cognitive depression organization is the means by which these subjects look at life events, as a consequence of their dysfunctional beliefs. According to recent cognitive models these beliefs are substantially helplessness or unlovability. These features appear early in childhood or adolescence when the person received recurring feedbacks of indifference, neglect or hostility from one or both parents. The dysfunctional beliefs may become intrusive in adulthood in the presence of excessive and/or protracted life stressors. Some people live with a constant attitude of sacrifice, application, seriousness and some of their choices are often supported by a sense of redeem. Given the recurrent high expectations and the energy invested in achieving them a fall-down is inevitable. Furthermore, a MDD is frequently observed among others Personality Disorders. Think of the Borderline Personality Disorders or of the Narcisistic Personality, these are the conditions in which a depressive episode will be severe and self-dangerous. Interpersonal sensitivity and neuroticism are also character traits that may explain the susceptibility to depression under particular circumstances. In conclusion there is a link between depression and personality or character, and this is the explanation of why everyone of us know friends, colleagues or parents that react in different ways when a problematic situation occurs like divorce, bereavement, loneliness, work or economic difficulties. These stressful situations might be well managed by the subject if they are time-limited. But when stressors become chronic and the subject has fewer and fewer resources, conditions for depression set in and personality traits may have minor relevance even for the features of depression.

Stress and Depression

In clinical settings patients often report one or more situations they had preceding the depressive episode and

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they attribute to said life events a causal relation to their depression. This is only partially true. Coping skills, which are related to personality and personal perception, are the turning point for understanding different responses from different people. What happens to our body during a depressive episode? Many tissues, neurotransmitters, hormones and cytokines work in order to produce a stress response, which is aimed at maintaining homeostasis.

Stress response is the result of the activation of the endocrine, nervous and immune systems which cooperate for the fight or flight reaction.

The most important anatomical structures involved are the hypothalamus, the pituitary gland and the adrenal gland. These structures constitute the Hypothalamic-Pituitary-Adrenal axis (HPA). Amygdala and prefrontal cortex also modulate the HPA axis. Major depression is strongly associated to an hyperactivity of the HPA axis [3-6]. In addition, during a depressive episode the hippocampus, the amygdala and several areas of the prefrontal cortex are decreased in volume, similarly to the response shown during stressful conditions.

When aversive stimuli become stressors two different responses are activated. The fast response is mediated by the CRH by comunicating with the sympathetic systems that employ releasing adrenalin and noradrenalin neurotransmitters, to a perceived dangerous event. In the mean time other peptdides called urocortins produce an anxiolitic response balancing the fight or flight CRH response. Both CRH and urocortins are regulated by glucocorticoids. The second response consists in the mobilization of the HPA, hypothalamus- pituitary-adrenal axis, which releases specific hormones in the systemic circulation. The hypothalamus has a central role in the modulation of releasing hormones by receiving neurons form the amigdala and other limbic areas (the emotional brain), that stimulate the pituitary gland which releases ACTH. At this level many control mechanisms such positive and negative feedbacks are involved. ACTH actives adrenal glands to produce the secretion of cortisol. The hyppocampus, with other limbic system areas, has two different kinds of cortisol receptors. The MR receptor is activated by normal levels of circulating cortisol. The GR receptor is activated when the cortisol levels get progressively higher, in the mean while hippocampus is genetically blocked. Cortisol hyperproduction and CRH overdrive determine an alteration in the balance of monoamines and lastly, neuronal atrophy. The acute stress response activates the monoamines, while the chronic stress determines a reduced activity of dopaminergic, serotoninergic and noradrenergic neurons. Persisting hypercortisolemia decreases serotonin synthesis. Thus antidepressants act not only as monoamines replacement but they also modulate brain's glucocorticoid receptors and the expression of MR and GR.

Furthermore, proinflammatory cytokines are also implicated in the development of depression such as interleukin-1α and β (IL-1α and IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). These cytokines are responsible for the manifestation of sickness behavior. Decreased movement, increased slow-wave sleep, altered cognition, social withdrawal and reduced food and water intake represent sickness behavior. However, there is no evidence supporting the idea that inflammation may explain pathogenic beliefs and their consequences such as sense of guilt, sense of failure or self-dislike [7].

In addition cytokines may activate IDO (indoleamine 2,3 dioxygenase) in macrophages, dendritic cells and other neurons, which degrade tryptophan along the kynurenine pathway [8, 9]. As a consequence there is low bioavailability of tryptofan, a precursor of serotonin in the brain. At the present time, it is not clear how this immune-mediated alteration of serotonin is activated, apart from the case of the inoculation of proinflammatory agents (IFNα) or particular medical conditions. Proinflammatory cytokines, glucocorticoids and their receptor have a negative effect on cellular plasticity, and neurogenesis. Indeed antidepressants works *via* the replacement of neurotransmitters and also by reducing the inflammatory state of the brain.

From an evolutionary perspective, depression (as well as social anxiety) can be explained in terms of motivational/behavioral systems with particular reference to the hierarchical system, and be viewed as a defensive response to positions or perceptions of low rank, defeat and entrapment. Humans as well as other primates in low status positions tend to be tense, vigilant to social threats, have high cortisol levels, lower 5-HT, display submissive behavior and experience shame [10]. Prolonged submissive behavior and the associated condition of chronic stress represent a conceptual link between biological markers of pathology and shame and negative self schemata.

GENETICS OF MAJOR DEPRESSION

Genes and non-shared environment are partially responsible to the etiology of Major Depressive Disorder (MDD). The classification of genes that empathize susceptibility for non-bipolar depressive disorders would be a major advance in the comprehension of pathophysiological mechanisms of MDD. The purpose of this section is to introduce the reader to current behavioural genetic studies of depressive disorders and to discuss possible future research developments in this area.

Genetic Epidemiology of MDD

Family studies investigating the degree of clustering of depressive conditions among genetically related family members found a higher-than-chance incidence of depression among first-degree relatives. Obviously, first-degree relatives share genes as well as the same family environment as genetic susceptibility. Twin studies suggest that genes account for 40-50% of the susceptibility to MDD in the population, although heritability might be higher in clinically identified probands [11].

The role of genetic factors originate from adoption studies. The most accepted hypothesis suggests that different genes interact to increase the individual's susceptibility and that a genetic effect on depression is probably due to specific gene-environment interactions [12].

Unipolar and bipolar (BP) mood disorders may share at least some genetic determinants, given the growing risk of MDD in the relatives of patients with BP. Data drawn from

separate twin samples with bipolar *versus* unipolar depression (MDD), suggested, however, that as much as 71% of the genetic tendency to mania is separate from the tendency to depression.

Association Studies of Candidate Genes

Monoaminergic Candidate Genes

Most candidate genes trials of depression focused on functional polymorphisms in a small set of genes involved in monoaminergic neurotransmission (DNA sequence variations that modify the expression and the functionary of the gene). Most of these genes are implicated in the synthesis, degradation, or neurotransmission of serotonin (5-HT). In particular, current research comprises the loci encoding the serotonin transporter (SLC6A4), the tyrosine hydroxylase (TH) (the limiting enzyme for dopamine synthesis), the serotonin 2A receptor (5HTR2A) and the tryptophan hydroxylase 1 (TPH1) (serotonin synthesis). Other genes that have been studied include the catechol-o-methyltransferase (COMT) (dopamine catabolism) and the dopamine (D4) receptor (DRD4).

5-HTTLPR, Depression, and Stress

The SLC6A4 gene encodes the serotonin transporter, which result in the "reuptake" of serotonin back into the presynaptic cell. The 5-HTTLPR, a polymorphism in the promoter region of the serotonin transporter gene SLC6A4, includes two different alleles: one long with 16 repeats (L) and one short with 14 repeats (S). The S allele correlated with a reduction in mRNA levels, serotonin binding and reuptake. Currently, a functional single nucleotide polymorphism (SNP) within the 5-HTTLPR variant has been identified to be responsible of the modification of the functional consequences of carrying the L allele. Furthermore, an adenine/guanine (A/G) SNP (rs25531) was described that is apparently within the 5-HTTLPR L allele sequence. This allele variant shows reduced activity similar to that of the S allele [13].

The 5-HTTLPR variant has been studied extensively for the possible association with mood disorders, anxiety and related personality traits. Several meta-analyses examined these polymorphisms in MDD, Bipolar Disorder (BD), suicidal behavior, and/or for neuroticism [14]. A modest association with BD, and with suicidal behavior and an association with depression-related trait scores (neuroticism) emerge from these trials. Meta-analyses, however, have not shown the association between this polymorphism and MDD. Moreover many studies tested the hypothesis of a significant interaction among 5-HTTLPR alleles or genotypes, depression, and stress (gene environment interaction); these studies supported an effect of 5-HTTLPR genotype on stress reactivity rather than directly on depression. The association between short alleles and depression, the onset of depression following low-threat events for the short-short genotype, the increased depression scores in maltreated children and the increased amygdale activation in response to stressor stimuli, underline the interaction between 5-HTTLPR, depression and stress [15]. However the exact mechanism of this association remains unclear [16].

Other Candidate Genes

Tryptophan hydroxylase (TPH) is an attractive candidate gene, because it is a key enzyme in the synthesis of serotonin. Recent trials underlined that the *TPH2* isoform (rather than *TPH1*) is dominant in the brain, and MDD is associated with one of 10 *TPH2* SNPs and with SNP haplotypes. A relationship between *TPH2* and somatic anxiety in unipolar depression, paroxetine response in depression and suicide, was underlined in several studies [17] In stressed conditions, other serotonergic genes are involved in modifying the risk for depressive symptom. Some studies underline the association between *5HTR1A* -an auto inhibitor of serotonin release- and MDD and emphasize higher depression rates associated with the G allele. One study reported that the A/G polymorphism in the promoter of *5HTR2A*, a mediator of the downstream effects of serotonin, is associated with MDD [18].

A further etiological hypothesis about depression comprehend the hypothesis that neurotoxic effects related to corticotrophin activity and cytokines inflammatory effects damage hippocampal cells, which is involved in the genesis of many depressive symptoms. The responses to stress can be modulated from genetic factors that could alter the balance of neurotoxic and neuroprotective effects, while antidepressants have been shown to enhance neuroprotective effects. *Brain-derived neurotrophic factor (BDNF)* is a neuroprotective protein, and some reports described a reduction of serum BDNF in MDD [19]. Only one report underline the association between the *Val66Met* polymorphism and neuroticism, but data for MDD are not available.

The hypothalamic-pituitary axis, is altered in patients with MDD; the *Angiotensin-converting enzyme (ACE)* was proposed as a candidate gene for MDD because it affects blood pressure. Few studies suggested an association between MDD and functional insertion-deletion polymorphism in ACE.

Separate meta-analyses have examined association of MDD with the gene encoding the *dopamine D4 receptor* (DRD4).

There is some evidence supporting an association between MDD and *methylenetetrahdrofolate reductase encoding (MTHFR)* gene, an enzyme implicated in the degradation of homocysteine. An increase of homocysteine is link to vascular inflammation and heart disease. Meta-analysis fails to support a significant association with this organic alterations and depression.

Some authors hypnotized an association between MDD and a functional polymorphism in *DISC1 (dysbindin-1)* [20], a gene associated with schizophrenia. Finally in a region of chromosome 12 some authors suggested that *APAF1 (encoding apoptosis protease activating factor 1)* may be an MDD candidate gene. Summarizing, because of our limited understanding of the pathophysiology of MDD [21], other genes may play a role in the etiology of MDD.

Genetic Linkage Studies

Few studies found convincing evidence for linkage (genome-wide level significance), and there was little replication across studies for regions suggestive of linkage. Few

studies highlight that for MDD, only the short arm of chromosome 1 (1p) contained linkage signals. Genetic epidemiological studies support the association between anxiety disorders and personality traits and confirm that neuroticism is genetically related to MDD. A number of linkage scans for these phenotypes have identified genomic regions that overlap those from scans involving MDD. One study identified the linkage of the CREB1 region of 2q to Mood Disorders [22], and another study pointed out the presence of an MDD predisposition gene on chromosome 12q22-q23.2 [23]. Recently several trials showed the importance of epigenetic factors that leads individuals to a susceptibility to environmental adversities [24-26].

NEUROBIOLOGICAL FACTORS ASSOCIATED WITH DEPRESSION

In the pathofisiology of MDD is involved the neural systems, the emotion processing, the reward seeking, and the regulate emotion system [27]. The structures involved in emotion and reward processing are the amygdala, the ventral striatum, the medial prefrontal and anterior cingulate. The cortical regions are involved in processing emotion, and lateral prefrontal cortical systems that include the ventrolateral prefrontal cortex and the dorsolateral prefrontal cortex, are associated with the cognitive control and the voluntary or effortful regulation of emotion [28]. The medial prefrontal-limbic network, including amygdala, anterior cingulate cortex, and medial prefrontal cortex is modulated by serotonin neurotransmission; the reward network that include the ventral striatum and interconnected orbitofrontal and medial prefrontal cortices is modulated by dopamine. In these neural systems in adults, neuroimaging studies have provided evidence for specific abnormalities.

Over the past two decades, various hypotheses have been debated and three main neurotrasmitters, norephinephrine, dopamine, and serotonin have long been considered in the pathophysiology and treatment of mood disorders, although other neurotransmitter systems may as well be involved in mood disorders [29].

Noradrenergic Neurons

Norepinephrine, also known as noradrenalin, is a monoamine or catecholamine that consists of a single amine group and a catechol nucleus (a benzene ring with two hydroxyl groups). It is present both the central and peripheral nervous systems. Norepinephrine is the main neurotransmitter released by the sympathetic nervous system and mediates the "fight or flight" reaction. Among its functions is to prepare the body for action by affecting cardiovascular function, gastrointestinal motility and secretion, bronchiole dilation and glucose metabolism. Norepinephrine has been associated with several brain functions in the central nervous system, including sleep, memory, learning, and emotions.

Noradrenergic neurons are mainly present in the *locus coeruleus* (LC) that is the primary source of the noradrenergic innervation of the forebrain. The LC provides the sole source of NE to hippocampus and neocortex, critical regions for the cognitive and affective pro-noradrenergic system and projects to areas of the brain and spinal cord. The inputs to the LC are complex; in addition LC extensively innervates the cerebral cortex, the limbic system, the basal forebrain (medial septal area, medial preoptic area) and the thalamus, especially the dorsally located nuclei.

The NE receptors are categorized in alpha 1A, 1B, 1C or alpha 2A, 2b, or 2C or as beta 1, beta 2, or beta 3. Alpha 1 receptors are generally leads to excitation of the follower cells.

Serotoninergic Neurons

The serotonergic neurons play a main role in the integration of behavior; serotonergic neurons project to every part of the central nervous system (the brain and spinal cord) influencing the transmission of all the other neurotransmitters. Most serotonin is found in the enterochromaffin cells in the gastrointestinal tract involved in the regulation of intestinal movements. The *raphe nuclei,* distributed in the reticular formation, is the principal source of serotonin release. Axons from the lower *raphe nuclei* terminate in the spinal cord as well as in the cerebellum's deep nuclei and in the cortex and axons from the higher *raphe nuclei* terminate in subcortical nuclei that include *thalamus, corpus striatum*, *nucleus accumbens*, *hypothalamus, hippocampus, amygdala*, and in *cingulate cortex*, including the *cingulum*, the *corpus callosum* , the *hippocampus*, and the *neocortex.*

Seven distinct families of 5-HT receptors have been identified (5-HT1–5-HT7) and subpopulations have been shown for several of these. Actually at least 15 subpopulations have been cloned. The multitude of 5-HT receptors allow a better understanding of the different and complex processes in which 5-HT is involved.

Dopamine Neurons

Dopamine (DA) was described as an important neurotransmitter of the central nervous system half a century ago. Its role in movement control has long been demonstrated in patients affected by Parkinson's disease (PD). It is now well known that DA is involved in reward system and in the neurobiology and symptoms neurological and psychiatric diseases, including schizophrenia and attention deficit hyperactivity disorder.

Dopaminergic neurons are an heterogeneous group of cells concentrated in the *mesencephalon*, in the *diencephalon,* in the *cerebral cortex*, in the *olfactory bulb* and in the *spinal cord*. However, the ventral part of the *mesencephalon* contain almost all DA cells. The nigrostriatal system, which originates in the SNc and presents into the *caudate-putamen nucleus*, is involved in the control of voluntary movement. The DA system includes the mesolimbic and mesocortical pathway, which arise from VTA; they have been suggested to modulate emotion-related behavior. The mesolimbic dopaminergic system include VTA that project to the *nucleus accumbens* (NAc) and to the *olfactory tubercle* innervating *the septum, amygdala and hippocampus*. The mesocortical dopaminergic system projects to the *prefrontal, cingulate* and *perirhinal cortex*. From their different nuclei, dopaminergic axons progress medially where they join together and project through the median forebrain bundle (MFB) to the internal capsule. SNc neurons send projections to the *caudate* and *putamen nuclei (striatum),* named the nigrostri-

atal system. Dopaminergic axons originating in the VTA innervates to the ventral part of the striatum, a region named NAc.

The heterogeneous physiological actions of DA are mediated by five distinct G protein-coupled receptor subtypes that present a similar pattern of distribution that dopaminergic fibers.

Monoamine Hypothesis for the Etiology of Depression

The first etiological hypothesis postulated to explain symptoms of depression was the monoamine hypothesis. This hypothesis, derived from the observation that agents acting on the synaptic concentrations of monoamines can improve symptoms of depression, suggests that depletion of monoamine neurotransmitters is the main cause of depressive symptoms. Currently the most popular hypothesis for the etiology of depression seems to involve the monoaminergic receptors and the downstream molecular events that this receptors trigger, including the gene expression. This theory postulates that the depletion of neurotransmitters causes compensatory upregulation of postsynaptic receptors and that there is a defect in downstream signal transduction of the monoamine neurotransmitter and receptor. At molecular level the abnormality would be in the signal transduction cascade system and in appropriate gene expression.

For the diagnosis of major depression numerous symptoms are required. Each symptom is hypothetically associated with inefficient information processing in various brain circuits [30]; some brain regions in depression, in fact, have enhanced neuronal activation, while others have reduced neuronal activation. Nevertheless, main antidepressant treatments available today all generally act on one or more of these neurotransmitter systems.

Other Neurotransmitter Alterations

In the pathophysiology of depression, an increasing interest has been attributed to the glutamatergic system. Glutamate is the primary excitatory neurotransmitter in the central nervous system. A dysfunction or reduced number of glia cells, important regulators of the glutamatergic metabolism, was observed in patients suffering from depression. This could cause an hyperfunctioning of the glutamatergic system and a toxic increase of glutamate Antidepressants used in clinical practice modify the glutamate metabolism and some clinical trials [31] shown that antiglutamatergic substances (riluzole) and NMDA-receptor antagonists (ketamine) possessed antidepressant properties.

Neuron fibers containing acetylcholine (ACH) are distributed throughout the cerebral cortex and interact with monoamine and glucocorticoid systems. ACH neurons have alerting or activating acute effects on brain systems. The two principal subtypes of ACH receptors are called nicotinic and muscarinic receptors. Drugs with agonist and antagonist effects on ACH have opposing effects on depressive symptoms. Behavioural changes following administration of an ACH agonist include lethargy, anergia, and psychomotor retardation in normal subjects, and in patients, exacerbation of depression [32].

Increasing evidence propose that the neurobiology of depression is associated with abnormalities in amino neurotransmission. Gamma-aminobutyric acid (GABA) has inhibitory effects on NE and DA pathways. Chronic stress can reduce or deplete GABA levels in some regions of the brain. Several studies reported that depressed patients have lower GABA concentrations than non-depressed subjects. The interest in these findings also increased due to the evidence that several anticonvulsant and GABA-mimetic agents has mood stabilizing and antidepressant characteristics [33].

DISCUSSION

The etiopathogenesis of depressive disorders is always complex and multifactorial. There is a strong genetic and family component. In addition to the neurochemical hypothesis based on the use of antidepressants acting on monoamine neurotransmission, we briefly mentioned the organic hypothesis and the correlation between depression and organic diseases. In conclusion, the currently available data seem to support the hypothesis that some people are biologically predisposed to depression (genetics that affects neurotransmitters, CNS disorders), but on this predisposition are engrafted temperamental, attachment styles and environmental factors.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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