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Epigenetic Modulation of Mood Disorders

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Abstract

Background: Mood disorders are expressed in many heterogeneous forms, varying from anxiety to severe major clinical depression. The disorders are expressed in individual variety through manifestations governed by co-morbidities, symptom frequency, severity, and duration, and the effects of genes on phenotypes. The underlying etiologies of mood disorders consist of complex interactive operations of genetic and environmental factors. The notion of endophenotypes, which encompasses the markers of several underlying liabilities to the disorders, may facilitate efforts to detect and define, through staging, the genetic risks inherent to the extreme complexity of disease state.

Aims: This review evaluates the role of genetic biomarkers in assisting clinical diagnosis, identification of risk factors, and treatment of mood disorders.

Methods: Through a systematic assessment of studies investigating the epigenetic basis for mood disorders, the present review examines the interaction of genes and environment underlying the pathophysiology of these disorders.

Results: The majority of research findings suggest that the notion of endophenotypes, which encompasses the markers of several underlying liabilities to the disorders, may facilitate efforts to detect and define, through staging, the genetic risks inherent to the extreme complexity of the disease states. Several strategies under development and refinement show the propensity for derivation of essential elements in the etiopathogenesis of the disorders affecting drug-efficacy, drug metabolism, and drug adverse effects, e.g., with regard to selective serotonin reuptake inhibitors. These include: transporter gene expression and genes encoding receptor systems, hypothalamic-pituitary-adrenal axis factors, neurotrophic factors, and inflammatory factors affecting neuroimmune function. Nevertheless, procedural considerations of pharmacogenetics presume the parallel investment of policies and regulations to withstand eventual attempts at misuse, thereby ensuring patient integrity.

Conclusions: Identification of genetic biomarkers facilitates choice of treatment, prediction of response, and prognosis of outcome over a wide spectrum of symptoms associated with affective states, thereby optimizing clinical practice procedures. Epigenetic regulation of primary brain signaling, e.g., serotonin and hypothalamic-pituitary-adrenal function, and factors governing their metabolism are necessary considerations. The participation of neurotrophic factors remains indispensable for neurogenesis, survival, and functional maintenance of brain systems.

Keywords: Epigenetics; Genes; Endophenotypes; SNPs; Staging; Serotonin; Glucocorticoid; BDNF; Drug therapy; Mood disorders

Introduction

Adverse fetal and early-life conditions that disturb normal brain development are associated with neuropsychiatric disorders, with emergent epigenetic changes [1,2] determining life-long susceptibility to chronic disease states [3,4]. Several major aspects influence the eventual individual developmental trajectories that possess an essential determinant modulating effect upon outcome of future intervention:

1. The type of agent that interferes with brain development, whether chemical, immune system-activating, or conspicuous through absence,
2. The phase of brain development at which the agent exerts disruption, i.e., prenatal-gestational, postnatal-infancy, adolescent, or adult lifespan,
3. The age of expression of structural-functional abnormalities with emotional, cognitive, and everyday behavior domains, and
4. The particular pharmacogenomics-pharmacogenetics profiles mediating responses to drug therapies [5] (Table 1).

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Site of Action	Gene	Promoter Region	Anomaly
Serotonin transporter	*SLC6A4*	5-HTTPLR	SSRI-efficacy
P-Glycoprotein	*ABCB1*	Upstream/downstream promoters	ABC-transporter[1]
CRH-receptor of HPA axis[2]	*CRHR1*	Luciferase reporter plasmid	Suicidality
5-HT_{2A} receptor	*HTR2A*	-1438G/A (rs6311)	Overdensity
Glucocorticoid receptor	*NR3C1*	Luciferase reporter plasmid	Stress adaptation
BDNF[3] neurotrophin	*BDNF*	Multiple promoters	AD-enhanced plasticity
AD-drug action	*MAGI2*, *DTWD1*. *WDFY4*, and *CHL1*	Multiple promoters	Symptom-exacerbation

[1]Transportation of a wide variety of substrates across extra- and intracellular membranes
[2]Corticotrophin-releasing hormone (CRH) of the hypothalamic-pituitary-adrenal axis (HPA)
[3]Brain derived neurotrophic factor (BDNF)

Table 1: The pharmacogenetics of certain genes associated with the pathophysiology or efficacy, metabolism, or availability of pharmacotherapeutic agents in mood disorders.

Among the mood disorders, adolescent depression is considered relatively common with prevalence ranging from 5% [6] to about 14-15% in the United States of America [7], and may predict adult depression [8]. Female sufferers from the disorder remain almost twice as many as male sufferers with the relative gender proportions evident already during adolescence [9]. Complex traits such as susceptibility to diseases are determined in part by variants at multiple genetic loci. Genome-wide association studies can identify these loci, but most phenotype-associated variants lie distal to protein-coding regions and are likely involved in regulating gene expression [10]. Quality-of-life and psychological health are increasingly found to be intimately related [11]. A study of adolescents' personality and intentional happiness-increasing strategies as a function of temperament and character, as phenotypes [12], showed that the harm-avoidance and self-directedness dimensions predicted subjective well-being. A mediating factor was a strategy endorsing ambivalent effort to both avoidance and mobilization of negative thoughts and feelings. The dynamic nature of epigenetic mechanisms holds implications not only for psychological health and well-being but also eventual therapeutic interventions focused upon mood disorders [13,14].

The aim of the present review was to examine the interactions of genes and environment in contributing to the pathophysiology of mood disorders. This was performed through a systematic review of articles and abstracts (where articles were not available) identified through PubMedicus. Relevant key words of interest were epigenetics, genes, endophenotypes, SNPs, staging, serotonin, glucocorticoid, BDNF, drug therapy, and mood disorders.

Mood Disorders, Genes, Pathophysiology and Environment

Every-day mood is influenced by circadian rhythms and stress with risk for disorder dependent upon a combination of factors, such as predisposition and vulnerability as defined by genetic parameters, early life events, and consequences of later life events. Life-event coping is linked to biological stress responses that vary from person to person according to set-points determined genetically and epigenetically during juvenile years and involve the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Both flexibility in coping and a chronic cortisol exposure in brain regions regulating affect and cognition are relevant to expressions of mood disorders. Additionally, gender differences in mood disorders are influenced by several personal and environmental factors, including physiological changes experienced during puberty, experienced-shift in social roles, affiliations and expectations regarding peers and adults, and transient affective status that may provide negative/stressful experiences [15-17]. Edwards et al. [18] have shown that the magnitude of environmental influences upon depressive symptoms during adolescence changes as a function of pubertal development, the timing of which differs across gender. Age may contribute a modulating influence on mood disorder: Among older women, Gillespie et al. [19] obtained evidence that both depression and anxiety interacted reciprocally with disrupted sleep, whereas among younger women both depression and anxiety appeared to have a causal impact on sleep. Finally, Edwards et al. [20,21] suggested that mood disorders genetically and environmentally correlated across adolescence. Brain-body epigenetic machinery poses a highly complicated and intertwined arrangement of predisposing and randomly-occurring factors, thereby emphasizing the necessity for further refined studies to disentangle brain-region and cell-type specific epigenetic codes under specific environmental conditions [22].

The consequences of multiple gene interactions with environment and each other through complex mechanisms, such as genetic heterogeneity and polygenicity, in combination with phenotypic variation, underscores inestimable individual differences in symptom severity, frequency, durability, manifestation, and co-morbidity in mood disorders [23]. Moreover, an important influence on outcome for future intervention is the pharmacogenomic-pharmacogenetic profile mediating responses to drug therapies. Table 1 provides examples of the pharmacogenetics of certain genes associated with the pathophysiology or efficacy, metabolism, or availability of pharmacotherapeutic agents in mood disorders.

Developmental plasticity, from preconception to early childhood, involving epigenetic responses to environmental changes exerted during life-history phase transitions, modulates brain development and cell- and tissue-specific gene expression, and may be transmitted transgenerationally [24]. Several genetic polymorphisms influencing treatment outcome, and environmental exposures in early life, such as childhood maltreatment, exert long-lasting influences that are

moderated by inherited genetic variation and mediated through stable epigenetic mechanisms such as tissue- and gene-specific DNA methylation [25]. Epigenetic mechanisms reflect the sensitivity and responsiveness of the brain and nervous system to variations in environmental circumstance, thereby modulating gene expression to the biomarkers and phenotypical outcomes that describe individual profiles [26,27]. Most epigenetic alterations are independent of genetic alterations yet interactions on specific genes, signaling pathways, and within chromosomal domains, in combination with genomic and epigenomic profiling manifest avenues for further comprehension of brain disorders. Symptom-profiles and disease course, etiopathological heterogeneity, and etiopathogenesis may be clarified by a dimensional approach to pathophysiology through the distinction of endophenotypes and concomitants of disease progression. Several lifestyle factors, among which are diet, obesity, physical activity, tobacco smoking and second hand smoke, alcohol consumption, drug abuse, environmental pollutants, psychological stress, and working on night shifts, can modify epigenetic patterns. To achieve an understanding of the mood disorders, genomic approaches must be complemented by a variety of strategies, including phenomics, epigenomics, pharmacogenomics, and neurobiology, as well as the study of environmental factors.

Mood disorders are an associated group of diagnoses in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV TR) classification system, wherein a disturbance in the person's mood, or emotional or affective status, is considered to present the main underlying feature [28]. Both unipolar depression and bipolar disorder present clinically severe conditions characterized by recurring episodes of depressive symptom categories, and in the latter periods of mania, with a life-long lasting prevalence [29-31]. It has been suggested that whereas mood refers to the underlying or longitudinal emotional state, affect pertains to the external/visible expression of the individual observed by others [32]. Unipolar depression and bipolar disorder, of the depressive disorder spectrum of mood disorders, present severe illnesses and are leading causes of disability and suffering among a large population of afflicted individuals [33]. Mood disorders describe less severe forms of depressive disorders, yet although less extreme, dysthymic disorder induces long-lasting moodiness expressed through low, dark moods. Dysthymic disorder may occur by itself or in co-morbid relation to other psychiatric, e.g., drug abuse, or mood disorders [34-36]. Both anxiety and depression are markedly co-morbid and present strong relationships in continuous scale formats [37-39]. These disorders are associated with marked negative effects upon work relationships and performance, attendance, daily functioning, and care-givers situations, with overall increases in costs accumulating from loss-of-productivity, etc. [40-42]. Epigenetic mechanisms altering the activities of genes mediated through early life experiences leave indelible chemical marks within brain tissue thereby influencing both physical and neuropsychiatric health [43].

"Anxiety-sensitivity," a lowered threshold for expression of physical and emotional anxiety symptoms, is a risk factor for mood disorders in children and adults [44,45], with multiple dimensions [46,47]. Factor analysis from a large study of adolescents has implicated a hierarchical structure for anxiety-sensitivity; all of its dimensions are derived from a higher-order, general anxiety sensitivity factor. The hierarchical model consists of three dimensions: Physical, Social, and Mental anxiety-related incapacitation concerns [48]. Other observations have confirmed the anxiety-sensitivity model [49]. Zinbarg et al. [50] have provided results demonstrating that anxiety-sensitivity-Physical Concerns is the only one of the three anxiety-sensitivity group factors that contributes to relations with fear responses, whereas anxiety-sensitivity-Mental Incapacitation Concerns produced a stronger positive linear association with depressed mood than did anxiety-sensitivity-Physical Concerns. In a self-report study of three test-time points from adolescence to young adulthood with 2651 participants from the G1219 twin study, Brown et al. [51] also obtained a three-factor model that depicted the Physical, Social, and Mental anxiety-related incapacitation concerns. However, the findings were characterized by higher levels of interpretability and parsimony than previously reported. The researchers found that multivariate genetic analyses supported a hierarchical structure with general genetic and non-shared environmental influences.

In summary, mood disorders present as disturbances in emotional feelings or affective states. A variety of genetic, pathophysiological, and environmental factors play important roles in determining the risk factors for mood disorders, including early childhood experiences. Moreover, treatment outcome is related to particular pharmacogenomics-pharmacogenetics profiles mediating responses to drug therapies.

Serotonergic Regulation

Epigenetic mechanisms regulated the effects of early life stress in Rhesus macaques upon serotonin transporter (5-HTT). In his nonhuman primate model, Kinnally et al. [52] showed that 5-HTT cytosine-phosphate-guanosine methylation was an important regulator of 5-HTT expression in early life contributing to risk for mood disorders that were observed in "high-risk" serotonin transport gene polymorphism 5-HTTLPR carriers. The identification of the particular relationships between genotype and drug response, including both the therapeutic effect and side effect profile, will influence the medical practice of disorder-intervention to a degree as yet impossible to assess. Despite the huge application of antidepressant (AD) compounds to afflicted individuals, only 60% of those treated with these drugs show sufficient response to medication, and adverse effects are common while numerous pharmacogenetic studies point to the involvement of genetic factors. Studying the effects of corticotrophin-releasing factor (CRF) overexpression as a basis for serotonergic-HPA axis interaction, Flandreau et al. [53] observed that amygdala CRF overexpression increased anxiety-like behavior in the defensive withdrawal test of rats at week eight, which was only partially prevented by the selective serotonin reuptake inhibitor (SSRI) citalopram. They found that in both CRF-overexpressing rats and control groups, citalopram decreased hippocampal CRF expression with concomitant increases in hypothalamic and hippocampal expression of the glucocorticoid receptor. The gene expression altered was considered to be associated with a significant decrease in HPA axis reactivity in rats treated with citalopram. Furthermore, citalopram increased the rate of weight gain only in rats over expressing CRF. Taken together, it may be argued that chronic AD treatment with SSRIs presented an epigenetic factor affecting outcomes as a function of CRF over expression.

The therapeutic response to ADs is marked by inter-individual variability, and a large proportion of patients with major depressive disorder do not response adequately to the first AD drug prescribed [54]. Therefore, identification of genetic biomarkers that predict AD treatment response likely would improve current clinical practice. Studies on AD treatment response have focused on both aspects of pharmacogenetics research, i.e., identifying new candidate genes that may predict better treatment response for patients [55], and taking into account the situation that AD drug response aggregates in families

[56]. Narasimhan and Lohoff [57] have reviewed recent findings on the pharmacogenetics of AD drugs and future clinical applications. The individualization and optimization of treatment decisions for unipolar depression couched in terms of "the right drug/treatment for the right patient" remains restricted, in part because sufficiently powerful clinical or biological predictors are missing [58]. The relevance of personalized medicine is illustrated graphically by evidence emerging from studies of the fate of serotonin released into the synaptic cleft. That is, dysfunctions of serotonergic neurotransmission are involved in the physiopathogenesis of mood disorders. Serotonin concentration in the synaptic cleft is essentially regulated by the serotonin transporter (5-HTT), and in this regard, a length polymorphism repeat in the 5-HTT promoter region, termed 5-HTTLPR, has been linked to the disorder. From a German genome-wide association data set, Haenisch et al. [59] detected a significant association between the TA haplotype (tagging the S-allele of the 5-HTTLPR) and mood disorder, and this is consistent with previous findings of an association between the 5-HTTLPR S-allele and mood disorder [60].

Contributory factors to the higher prevalence during adolescence of depressive symptoms and mood disorders among girls compared to boys are age-at-onset and onset of puberty [61-63]. Edwards et al. [18] have showed that that pubertal development moderates environmental influences on depressive symptoms. At 14 years of age, more developed girls, relative to their less developed peers, were more likely to have depressive symptoms, but this decreased in influence by age 17. The effects observed in boys were similar, but are delayed, paralleling the delay in pubertal development in boys compared to girls, and thereby supporting the premise that environmental influences on depressive symptoms during adolescence changes as a function of pubertal development. Joinson et al. [64] found that depressive symptoms among girls during mid-adolescence were more strongly influenced by breast stage than timing of menarche. This implies that the female rise in depression during adolescence may be due to increasing levels of estrogen, and may account for the gender difference in rates of depression at this stage. Nilsen et al. [65] performed a systematic review of 32 anxiety studies and 13 depression studies that met predefined methodological criteria comprising client demographic characteristics (age, gender, ethnicity, IQ) and clinical factors (duration, type of diagnosis, pre-treatment severity, co-morbidity). Most of the studies showed non-significant associations between demographic factors (gender and age) with treatment outcome for both the anxiety and the depression treatment trials. The anxiety studies showed mainly the lack of demographic or clinical factors predicting or moderating treatment outcome. In the case of depression studies, the findings implied that baseline symptom severity and comorbid anxiety might impact treatment response. Gender differences in response to intervention other than medication may be revealing: Gender and crime victimization significantly modified treatment effects on distress and a behavioral-problems index [66]. Adolescent girls in families without crime victimization benefited from moving-to-opportunity intervention for all outcomes, distress, and major lifetime depressive disorder. Adolescent boys in intervention families experiencing crime victimization expressed worse distress, more behavior problems, and somewhat higher major lifetime depressive disorder versus controls. Finally, a community-based longitudinal sample of 309 adolescents reported depressive symptoms and negative life events at ages 11, 13, and 15. In a study by Priess-Groben and Hyde [67], 5-HTTLPR and MAOA-uVNTR genotypes were ascertained via buccal swabs. The significant four-way interaction between 5-HTTLPR, MAOA-uVNTR, NLE at age 13, and gender predicted depressive symptoms at 15 years of age whereby girls were most likely to exhibit elevated depressive symptoms when experiencing negative life events if associated with low-expression MAOA-uVNTR alleles and short 5-HTTLPR alleles. For boys, low-expression MAOA-uVNTR alleles but long 5-HTTLPR alleles were implicated. Taken together, the existing observations of pre-treatment patient variables as predictors and moderators of anxiety and depression treatment outcome provided little consistent knowledge concerning for what type of patients and under what conditions treatments work.

Keers [68] has suggested that gene-environment interaction studies may provide an explanation for the above discrepancies regarding the 5-HTTLPR locus and the actions of SSRIs, particularly involving the interaction between stressors and 5-HTTLPR. Gene-by-environment interaction effects were observed for genes encoding components of the hypothalamic-pituitary-adrenal axis. The T allele of rs1360780 in FKBP5 increased the risk of posttraumatic stress disorder (PTSD) following childhood maltreatment and rs10402 (a single-nucleotide polymorphism in the gene encoding CRHR1) and moderated the effects of this maltreatment on several behavioral phenotypes, such as alcoholism, neuroticism, and depression. This finding underlines the possibility that several polymorphisms moderate the effects of environmental adversity on the development of depression and treatment response [69]. Additionally, it has been found that individuals possessing the S allele experienced more depressive symptoms, clinical depression, and suicide attempts following recent stressful events or childhood maltreatment/adversity than those individuals carrying the L allele [70].

Bukh et al. [71] recruited a sample of 290 patients diagnosed with a single depressive episode, and using structured interviews, assessed the outcome of AD treatment and the presence of stressful life events during a six-month period preceding onset of depression. Nine polymorphisms in the genes encoding the serotonin transporter, brain derived neurotrophic factor, catechol-O-methyltransferase, angiotensin converting enzyme, tryptophan hydroxylase, and the serotonin receptors 1A, 2A, and 2C were genotyped. No evidence was forthcoming in support of the idea that the effects of the genetic polymorphisms on treatment outcome were dependent on stressful life events experienced by the individual prior to onset of depression [72]. Keers et al. [73] observed that stressful/adverse life events predicted a marked more effective response to citalopram, but showed no effect on response to nortriptyline; variation in the 5-HTTLPR promoter region polymorphism and another polymorphism in the gene, STin4, significantly modified these treatment effects. The serotonin transporter gene, *SLC6A4*, encodes the protein responsible for serotonin reuptake from the synaptic cleft following release from serotonergic neurons. The association between AD-induced mania and candidate genetic variants, focusing upon the promoter polymorphism of *SLC6A4*, has been examined [74]. Nevertheless, on the basis of a meta-analysis, Biernacka et al. [75] in attempting to confirm an association between the serotonin transporter gene polymorphism 5-HTTLPR (see above), and AD-induced mania, concluded that there was insufficient evidence.

Generalized anxiety disorder, a highly prevalent chronic neuropsychiatric disorder with marked morbidity and mortality. It is characterized by excessive, uncontrollable and often irrational worry about everyday things that is disproportionate to the actual source of worry, and symptoms that interfere with everyday behaviors persist for at least six months [76]. For both acute and chronic treatment, AD compounds with 40-70% treatment response are prescribed [77-79]. The 5-HT_{2A} receptor is expressed widely throughout the central

nervous system, particularly near most of the serotonergic terminal rich areas, including neocortex (mainly prefrontal, parietal, and somatosensory regions), and the olfactory tubercle, and is coded by the *HTR2A* gene. Links between the A-1438G (rs6311) polymorphism and mood disorders have been obtained [80], and several studies have found associations between the rs7997012 and rs17288723 single nucleotide polymorphisms (SNPs) and AD treatment outcome in patients presenting depression spectrum disorders [81-83]. Venlafaxine is a serotonin-norepinephrine reuptake inhibitor for treatment of major depressive disorder, generalized anxiety disorder, and comorbid indications. Lohoff [84] tested whether or not rs7997012 polymorphism predicted treatment outcome in 156 patients with generalized anxiety disorder. During their six-month open-label clinical trial administering venlafaxine XR (extended-release), they also obtained scores on the Hamilton Anxiety Scale and the Clinical Global Expression of Improvement scale. The frequency of the G allele differed between responders (70%) and nonresponders (56%) at six months on the Hamilton, and the G allele was associated with improvement. Similarly, Lohoff et al. [85] studied the interaction between SLC6A4 5-HTTLPR/rs25531 haplotype and rs7997012 polymorphism for venlafaxine XR in an 18-month relapse prevention trial comprising 112 patients. Patients with genotypes La/La + G/G or La/La + G/A (n=28) showed lower Hamilton scores than those with genotypes La/S +A/A or S/S +A/Aat six months, thereby concluding a gene-gene interaction between these markers.

Hypothalamic-Pituitary-Adrenal Axis (HPA) Regulation

Clinical and laboratory studies have shown that biological stress systems are shaped by adverse environments to instigate functioning in epigenetic systems with consequences for brain maturation under disorder conditions. Cortisol effects are exerted through glucocorticoid and mineralocorticoid receptors, with extremely high densities of glucocorticoid receptors in the hippocampus, dentate gyrus, prefrontal cortex, paraventricular nucleus of the hypothalamus, and amygdala, and mineralocorticoid mainly in the hippocampus, prefrontal cortex, and amygdala [86]. Both glucocorticoid and mineralocorticoid are co-expressed in the limbic system with balanced functioning in stress response regulation [87]. FKBP5 (FK506 binding protein 5), a protein encoded by the *FKPB5* gene and involved in immunoregulation, is implicated in posttraumatic stress disorder, depression, and anxiety [88,89]. FKPB5 SNPs interact with childhood trauma to predict severity of adult PTSD [90]. As a co-chaperone of glucocorticoid influences [91], its activity and alleles associated with enhanced expression of FKBP5 following glucocorticoid activation induce increased glucocorticoid resistance with reduced efficiency of the negative feedback of the stress hormone axis in healthy controls. This causes a prolongation of stress hormone system activation following exposure to stress [92]. Tyrka et al. [93] addressed the potential role of polymorphisms in genes regulating the HPA axis, thereby affecting putatively AD drug efficacy. Glucocorticoid is encoded by the NR3C1 gene on chromosome 5, which has three protein domains: immunogenic, DNA, and ligand-binding, as well as several functional genetic polymorphisms [94]. Relevant to mood disorders, SNPs in the region encoding the immunogenic domain involving changes in glucocorticoid function, linked to glucocorticoid-resistance syndromes, have been identified, e.g., ER22/23EK [95], which induces loss of glucocorticoid-sensitivity [96]. An overrepresentation of the ER22/23EK allele conferring glucocorticoid resistance has been reported [97,98]. N363S and BclI polymorphisms are associated with hypersensitivity to glucocorticoids, whereas the ER22/23EK polymorphism is related to glucocorticoid resistance. Both BclI and ER22/23EK polymorphisms were associated with susceptibility to develop major depression [97], while the ER22/23EK polymorphism was associated with a faster clinical response to AD treatment.

Longitudinal studies of abuse and neglect indicate the increased risk of cognitive impairment, social and emotional difficulties, and elevated risk for neuropsychiatric and physical disorder [99]. Conditions manifested by PTSD evidence abnormal functioning of frontal brain systems [100] and smaller cerebral and cerebellar volumes related to earlier onsets of abuse and longer durations of abuse [101]. Early life stress exerts long-lasting, even permanent, effects upon hippocampus associated cognitive functioning [102]; this regime disrupts development of neural systems mediating reward-related behaviors [103]. Horstmann and Binder [104] have argued that despite the glucocorticoid measures and presence of polymorphisms involving the stress hormone system showing associations with response to ADs, necessary concurrent assessment of several clinical, biomarker, and pharmacokinetic variables is required, before a suitable level of predictability is achieved. Nevertheless, the structure-function relationships of the HPA axis with regions involved in stress coping or non-coping, and the dynamics of the glucocorticoid system, are critical to notions concerning epigenetic influences on the etiopathogenesis of mood disorders [105] and predicting AD treatment response [106,107]. Compared to suicide victims who had not suffered neglect/abuse or healthy controls, suicide victims with a history of early childhood neglect/abuse displayed evidence of hypermethylation of the glucocorticoid gene promoter [108,109]. Suicide victims not exposed to early childhood adversity or patients afflicted by major depression only displayed no epigenetic marking of the hippocampus [110]. Thus, it is increasingly evident that epigenetic mechanisms mediate the gene-environment dialog in early life, thereby providing persistent epigenetic programming of adult neurophysiology dysfunctions and dysregulations [111].

Glucocorticoid sensitivity is influenced by several aspects of mood. First, cortisol awakening rise, reflecting the natural response to waking-up, with 50-75% increases in cortisol within 30 min, is modulated by sleep patterns, seasonal variation, daily activities, health indicators, and stressors/trauma [112,113]. Patients presenting mood disorders show higher basal cortisol awakening rise levels [114-116]. Second, HPA axis challenge using the dexamethasone suppression test indicates non-suppression effects in mood disorder patients [117-119]. And third, scalp-hair cortisol is associated with dysregulations linked to mood disorder [120-122]. Genetic variations on the glucocorticoid gene *NR3C1* affect cortisol sensitivity [123]. Haplotype 4 (*TthIII*I + 9β) and haplotype (*TthIII*I + 9β + ER22/23EK) are linked to resistance for glucocorticoid [124], and polymorphisms are associated with a generally healthy type [125]. Haplotype 2 (*Bcl*I), haplotype 3 (*TthIII*I + *Bcl*I) and haplotype 6 are associated with hypersensitivity to glucocorticoids and cortisol [126]. Both the ER22/23EK and *Bcl*I polymorphisms are associated with higher risk for a depressive episode [127,128], and variable responses to AD treatment [129]. Mineralocorticoid gene SNPs involved in mood disorder included the V allele in the MRI180V SNP and -2G/C variant. The FKBP5 and CRH-R1 polymorphisms are associated with glucocorticoid resistance and reduced negative feedback of the HPA axis [92]. Epigenetic changes wrought by adverse environments showed lasting changes to HPA functioning [130,131] as well as mood disorders [132,133]. Spijker and Van Rossum [134] have outlined epigenetic changes, both early-in-life and *in vitro*, affecting the set-point and HPA axis regulation.

Mood disorders are associated with early adversity, often prenatal

traumatic stress [130,135,136], and frequently are accompanied by relative elevations of glucocorticoid stress hormones. The deregulation and the irregularity of the HPA axis presents a major aspect of symptom and biomarker profiles in depressive disorders [137-139], focusing on the role of elevated cortisol [140] and the putative AD-induced normalization of HPA function [141]. The biological stress response exerts essential functions in coping with life events, differing widely between individuals with genetically and epigenetically determined set-points during infancy and adolescence [142]. It is possible the depressive spectrum disorders constitute an adaptive defense mechanism to excessive stress/distress, with the HPA axis expressing a hub in brain stress circuits implicated in depressive sub-types [143]. Nevertheless, both the corticolimbic (prefrontal cortex-hippocampus-amygdala) and the reciprocal monosynaptic cerebello-hypothalamic connections, together with dense glucocorticoid binding sites, play an important role in stress regulation and depressive disorder [105]. Piwowarska et al. [144] undertook to determine whether or not increased plasma concentrations occurred in patients with major depressive disorder as measured by the Hamilton Depression Rating Scale, and whether or not SSRI treatment with fluoxetine may re-regulate cortisol levels in a study of 21 patients (14 women; aged 29-75 years) and 24 healthy controls. Among patients responding to fluoxetine therapy (reduction of Hamilton scores by at least 50%), levels of cortisol were decreased. In mood disorders, higher mean cortisol levels and higher cortisol-awakening rise indicate hyperactivity of the HPA axis and dysregulated glucocorticoid sensitivity determined in part by polymorphisms in genes encoding receptors and proteins involved in HPA axis regulation [124,127,145]. Spijker and van Rossum [134] have outlined both genetic and epigenetic changes influencing the set point and regulation of the HPA axis, with major effects upon mood states that could originate from traumatic experiences *in utero* and during infancy [109,146].

Both the release of CRH and arginine vasopressin in the parvocellular neurons of the paraventricular nuclei of the hypothalamus mediate parallel activation of the sympathetic nervous system and the HPA, in turn activating proopiomelanocortin synthesis, processed to adrenocorticotrophin hormone, which induces secretion of glucocorticoids from the adrenal cortex [87,147]. Glucocorticoids act through mineralocorticoid and glucocorticoid receptors. The former, high-affinity receptors, are implicated in the appraisal process and acute stress response onset, and the latter, low-affinity receptors, promote adaptation and recovery from stress [148]. Glucocorticoid signaling of the negative feedback process involves a complex arrangement of agents involving the transcriptional regulation of target genes [149]. Preclinical and clinical studies point to impaired mineralocorticoid and glucocorticoid signaling capacity coupled to over activity of the corticotrophin-releasing hormone and arginine-vasopressin systems [150]. The over activity of the HPA axis, expressed by hypercortisolism, adrenal hyperplasia, and abnormalities in negative feedback, characterizes the biological abnormality in melancholic depression. In depressive states, anterior pituitary CRH1 receptors are down-regulated and response to corticotropin-releasing hormone infusion is blunted while, on the other hand, vasopressin V3 receptors in the anterior pituitary express enhanced responding to arginine-vasopressin stimulation which influences HPA over activity [151]. Depressed patients showed elevated numbers of adrenocorticotrophin hormone [152] and cortisol [153] secretory pulses as expressed through increased plasma and urinary free cortisol [154]. These changes were accompanied by increased size of pituitary and adrenal glands [155]. During pregnancy, maternal cortisol promotes secretion of placental corticotropin-releasing hormone [156]. In a group of medication-free pregnant women presenting major depression (n=27) or not (n=38), O'Keane et al. [156] found that maternal cortisol concentrations correlated highly with corticotropin-releasing hormone secretion for all participants. Second trimester corticotropin-releasing hormone concentrations and mean evening salivary concentrations were significantly higher in the depressed women.

Neurotrophic Factors

Meta-analysis of association data of mood disorders suggests the role of particular genes posing genetic risk with differential expression evidence in brains of mood disorder patients, supporting the contributions of specific genes. The "neurotrophin hypothesis" of depression posits a role of brain-derived neurotrophic factor (BDNF) in depression, although it is unknown whether BDNF is more involved in the etiology of depression or in the mechanism of action of ADs. Accordingly, deficiency in neurotrophic support levels may underlie mood disorders such that elevation of neurotrophic status to normal levels engenders mood recovery. Castrén and Rantamäki [157] have provided an account on the role of BDNF and its receptors in depression and the AD response presenting a model whereby the effects of AD treatments may occur via a reactivation of activity-dependent and BDNF-mediated cortical plasticity. Wolkowitz et al. [158] observed that pre-treatment with SSRIs, BDNF levels were lower in depressed subjects than in controls, but these levels did not correlate significantly with the pre-treatment assessment of depression severity. Depression ratings improved with SSRI treatment, and BDNF levels increased with treatment. Changes in BDNF levels were not significantly correlated with changes in depression ratings. However, pre-treatment BDNF levels were directly correlated with AD responses, and patients who responded to treatment (≥ 50% improvement in depression ratings) had higher pre-treatment BDNF levels than did non-responders. These results confirm low serum BDNF levels in unmedicated depressed subjects and confirm AD-induced elevations in BDNF levels, but imply that ADs, in conjunction with correcting BDNF insufficiency, function through a permissive or facilitatory role of BDNF in the mechanism of action of ADs. In this context, network analysis of meta-analysis-generated candidate genes expressing differential response in patient brains identified signaling pathways and functional clusters implicated in genetic risk for mood disorders [159].

An association between Val66 allele and higher neuroticism has been found, whereas the Met allele was either linked to lower neuroticism [160] or had no association [161,162]. Nevertheless, significant associations have been reported between Met allele carriers and increased introversion [163], increased harm avoidance [164], and significant gene-gene and gene-environment interactions pertaining to anxiety- and depression-linked endophenotypes [165-167]. Lester et al. [168] reported findings from a sample of 374 anxiety-disorder children of European ancestry undergoing cognitive-behavior therapy, from whom DNA was collected from buccal cells with cheek swabs. Their treatment response was assessed at post-treatment and follow-up time points. No significant associations were observed between BDNF rs6265 and the response to psychotherapy. However, children with one or two copies of the T allele of NGF rs6330 showed a greater likelihood of relinquishing their primary anxiety diagnosis at follow-up. The recently discovered human BDNF Val66Met (BDNF(Met)) polymorphism may play a role in stress vulnerability through pharmacogenetic influences affecting molecular and structural mechanisms underlying the interaction. Yu et al. [169] observed that heterozygous BDNF(+/Met) mice displayed HPA axis hyperreactivity, increased depressive-like and anxiety-like behaviors, and impaired working memory compared with

WT mice after 7 d restraint stress. Also, BDNF(+/Met) mice exhibited more prominent changes in BDNF levels and apical dendritic spine density in the prefrontal cortex and amygdala after stress, related to impaired working memory and elevated anxiety-like behaviors. These depressive-like behaviors in BDNF(+/Met) mice were reversed selectively by acute administration of desipramine, but not fluoxetine. Interestingly, these selective behavioral, molecular, and structural deficits appear similar to the stress and human genetic BDNF(Met) polymorphism interaction. From an aspect of "personalized medicine" (see below) the finding that desipramine but not fluoxetine exerted AD effects on BDNF(+/Met) mice suggests that specific classes of ADs may be a more effective treatment option for depressive symptoms in humans with this genetic variant BDNF.

Anxiety mood disorders, highly prevalent and persisting into adulthood [7,170], often have childhood onset [171], accompanied by several deficits/problems [172-174] with risk for various states of future ill health [175-177]. High rates remission and treatment response are predicted by symptom severity [178], parental psychopathology [179], and co-morbid mood disorder [180]. Meta-analyses from association data of mood disorders has indicated the role of particular genes in genetic risk, and the integration of association data from meta-analyses with differential expression data in brains of mood disorder patients could heighten the level of support for specific genes [159]. Several lines of evidence imply mechanisms underlying the reported increase in anxiety-like behavior elicited by perturbation in BDNF signaling [181]. The secretion of BDNF is activity-dependent with reduced secretion linked to the effects of stress and mood disorders [182,183]; AD treatments generally elevate BDNF secretion [184,185]. In the functional rs6265 (Val66Met) polymorphism, the Met allele is associated with decreased activity-dependent BDNF secretion [186], structural brain abnormalities in limbic regions [187], impaired hippocampal activity [188], impaired associative fear learning [189], defective BDNF secretion, and increased anxiety-related behavior in knock-in mice [190]. The Met allele decreases BDNF transport, contrary to the superior functioning of the BDNF polymorphism (Val(66)Met) Val allele, and has been associated with worsened performance on several cognitive domains in euthymic bipolar-disorder subjects and controls. Manic patients with the Val allele (Met-) had higher Barrow Welsh Art Scale for creativity and neuropsychological test scores than Met+ carriers [191].

Pharmacogenetics of Mood Disorder Treatment

Epigenetics of mood disorder implies a psychopathological trajectory for disorder risk, invariably precipitated by environmental adversity and trauma [192]. Consequently, description and prediction of the extent to which the gene profiles of individuals affect their responses to pharmacogenetic therapeutic interventions may be achieved [193,194] through applied notions of genes, proteins, and SNPs [195]. Scharinger et al. [196] have described comprehensive evidence on the influence of serotonergic genes (*SLC6A4*, *HTR1A*, *MAOA*, *TPH2*) and BDNF on the following neural intermediate phenotypes: amygdala reactivity, coupling of amygdala-anterior cingulate cortex activity, volume of anterior cingulate cortex, hippocampal volume, and serotonin receptor 1A (5-HT1A) binding potential. Several factors contribute to the difficulties involving drug treatment efficacy, e.g., delay-of-onset of therapeutic effect and tolerance, and compliance issues [197]. Pharmacogenetic studies of psychometric outcome measures of drug response are hampered by small effect sizes. These may be handled through intermediate endophenotypes of drug response, as imaging studies suggest, thereby strengthening the relationship between genes and drug response, as well as providing new insights into the neurobiology of depression and individual drug responses. The pharmacogenetics of treatments for mood disorders may focus upon several aspects of drug action, including pharmacokinetics, neurotransmitter metabolism and metabolic enzymes, transporter mechanisms, etc. For example, Porcelli et al. [198] have focused upon genes linked to pharmacodynamics, and in the stratification of these identifications, have indicated several inconsistencies across observations. Scharinger et al. [199] have reviewed imaging genetics studies in mood disorders that apply complex genetic disease models, such as epistasis and gene-environment interactions, and their impact on brain systems regulating emotion processing and interventional outcomes. The notion of "differential-susceptibility" incorporates the specific genetic variants of individuals and the extent to which they are affected by environmental experiences [200-203]. Eley et al. [204] collected DNA from 584 individuals presenting anxiety-disorder and undergoing manual-based cognitive-behavior therapy, all with four white European grandchildren. They tested whether or not treatment response was associated with the 5-HTTLPR that was shown previously to moderate environmental influences upon depression [205]. They observed that children with the short-short allele genotype were significantly more likely to respond to cognitive-behavior therapy than those children carrying a long allele. In another study with adult bulimia-mood disorder co-morbidity patients [206,207], it was shown that the 5-HTTPLR short allele predicted a poorer treatment response whether or not cognitive-behavior therapy or medication or a combined therapy was administered.

Despite lack of molecular mechanisms for gene expression, P11 (S100A10), which is involved in intracellular transmembrane-trafficking of proteins [208], modulates neuronal function and is implicated in the pathophysiology of depressive disorders [209], with a role in regulation of how brain cells respond to 5-HT. In a laboratory model for gene therapy, p11 expression in mice was manipulated genetically by RNA interference. p11 was knocked down in the nucleus accumbens or in the anterior cingulate, and viral vectors were used to insert p11 into the nucleus accumbens of mice with knocked-out p11 [210]. The mice were then tested for laboratory expressions of depression-like behaviors (time of immobility in forced-swim and tail-suspension tests) and anhedonia (strength of sucrose preference). This was followed by measures of post-mortem human p11 concentrations in the brains of 17 depressed patients and 17 healthy age- and sex-matched controls. Restoration of p11 expression specifically in the nucleus accumbens of the p11 knockout mice normalized depression-like behaviors. Human nucleus accumbens tissue showed a reduction of p11 protein in the depressed patients. The results suggested that p11 loss in rodent and human nucleus accumbens may contribute to the pathophysiology of depression. Additionally, there are very high S100B protein expressions, ensuring neuro- and gliotrophin inducing plasticity, in white matter tracts that are involved in the pathogenesis and treatment of psychiatric diseases such as major depression [211]. ADs elevate p11 levels in brain regions and *P11* gene therapy was antidepressive: p11 concentrations were reduced in post-mortem brain tissues of patients presenting depressive disorder and by the expressions of depression-like behavioral phenotypes [212,213]. Moreover, AD compounds have been found to exert neurogenic effects in an AD action [214,215]. Schmidt et al. [216] utilized bacTRAP translational profiling to illustrate that layer 5 corticostriatal pyramidal cells expressing p11 (S100a10) were markedly and specifically responsive to chronic AD intervention. This response required p11 and included the specific induction of Htr4 expression. Cortex-specific deletion of p11 abolished

the behavioral responses to SSRIs, but did not lead to increased depression-like behaviors. Their findings identified corticostriatal projection neurons that were critical for the response to ADs, suggesting that the regulation of serotonergic tone in this single cell type may have a pivotal role in AD therapy. Melas et al. [217] have observed decreased p11 levels, associated with higher methylation in the promoter region, in the prefrontal cortex of Flinders Sensitive Line rats, a depression model. The p11 level was reversed to normal by chronic treatment with the SSRI, citalopram, and was associated with increased *P11* gene expression and reduced mRNA levels of DNA methyltransferases, Dnm1 and Dnmt3a that maintain forebrain DNA methylation. These studies pertain to epigenetic mechanisms underlying p11 involvement in AD interventions. Using the PubMed database of publications to mid 2011, Gvozdic et al. [218] reviewed the available literature on pharmacogenetics of AD response and side effects. They observed that several variants in candidate genes involved in the pharmacokinetics or pharmacodynamics of ADs, including association findings in the serotonin transporter gene *5-HTT*, serotonin receptor genes, a gene coding an efflux pump in the blood-brain-barrier (*ABCB1*), and genes involved in the HPA axis. They concluded that future studies ought to investigate comprehensively the functional-biomarker analyses and underlying pathophysiology in considerations of gene-gene and gene-environment interactions.

Adverse therapeutic drug reactions have played a critical role in determining the suitability of pharmacological treatment of patients on both individual and group bases, with passage of drug across the blood-brain barrier being a related issue that affects pharmacokinetics. P-glycoprotein (P-gp), an ATP-driven efflux pump with capillary location [219], recognizes or expels drugs, including ADs [220], and is encoded by the *ABCB1* gene. Laboratory studies indicate that penetration of the blood-brain barrier by ADs is dependent on P-gp functionality [221,222]. The relationship between *ABCB1* gene variants and response to AD treatment is unclear [223-225]. To study the association between *ABCB1* gene variants and adverse effects of AD compounds in a large cohort of patients presenting major depression, de Klerk et al. [226] used the Netherland Study of Depression and Anxiety to examine data concerning drug use and side effects. Six *ABCB1* gene variants were selected, 1236T>C, 2677G>T/A, 3435T>C, rs2032583, rs2235040, and rs2235015, and haplotypes. They found a significant association between the number of SSRI-related adverse drug effects and rs2032583, rs2235040, and a haplotype. Serotonergic effects, sleepiness, gastrointestinal complaints, and sexual effects were predicted by these variants and haplotype.

Conclusions

Epigenetic mechanisms linked with a variety of environmental factors that encompass several aspects of adversity alter developmental trajectories of personal cognitive-emotional profiles that elevate susceptibility for mood disorders by affecting normal brain development and regional integrity. The involvements of serotonergic and HPA axis regulation, and neurotrophic factors in the pharmacogenetics of mood disorders may be traced through sites of action, genes implicated, promoter regions, and the multitude of clinical expressions of disorder. Epigenetic aberrations can affect drug treatment by modulating the expressions of key genes involved in the metabolism and distribution of drugs as well as drug targets, thereby contributing to inter-individual variation in drug response. The observed epigenetic alterations, together with the epigenetic profiles of circulating nucleic acids, have great potential to be used as biomarkers for personalized therapy. Ivanov et al. [227] have reviewed an update of pharmacoepigenetics with respect to regulation of drug absorption, distribution, metabolism, and excretion (ADME) genes and drug targets, and an implicit utility for predicting inter-individual variations in drug response. Kroeze et al. [228] have concluded that serotonin transporter gene variation in humans affects the efficacy and side effects of SSRIs, whereas on the other hand, SSRIs generally do not affect serotonin transporter gene expression in nonhuman animals. Instead, SSRIs alter mRNA levels of genes encoding serotonin receptors, components of non-serotonergic neurotransmitter systems, neurotrophic factors, hypothalamic hormones, and inflammatory factors, thereby presenting one case-study for illustrating epigenetic modulation in mood disorder.

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