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The Neuroplasticity of Depression: How Antidepressants and Cognitive Behavior Therapy (CBT) can Reverse Depression

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ABSTRACT

Depression is a complex disorder influenced by biological, psychological, and environmental factors (Santarelli et al., 2016). Depression is one of the most common forms of mental illness worldwide (WHO, 2021), yet the pathogenesis of depression and the mechanism of how antidepressants reverse depression remain unclear (Liu et al., 2017). The symptoms of depression are evident to most individuals, but the symptoms' persistent nature remains a mystery to most. The four primary regions of the brain involved in depression are the Prefrontal Cortex (PFC), hippocampus, amygdala, and Anterior Cingulate Cortex (ACC) (Hayley et al., 2013). This review presents the prevailing literature on how antidepressants and Cognitive Behavior Therapy (CBT) can reverse depression. More specifically, this paper will examine the pathogenesis of depression (chronic stress model of depression); how the combination of antidepressants and CBT can help reverse depression (neuroplasticity theory of depression) and minimize relapse associated with depression. The neuroplasticity theory of depression is supported by evidence of decreased neuroplasticity in the hippocampus and PFC; decreased concentration of BDNF; and antidepressants increasing the concentration of BDNF and improving neuroplasticity in the hippocampus and PFC (Liu et al., 2017). The increase in BDNF promoting neurogenesis in the hippocampus and PFC also promotes neurogenesis in the amygdala, Ventral Tegmental Area (VTA), and Nucleus Accumbens (NAc) (Liu et al., 2017). The increase in neurogenesis in the amygdala exasperates depressive-like symptoms and is a primary reason for relapse (Hayley et al., 2013).

The first section of the paper reviews the stress model of depression and the disruption in structural neuroplasticity (Liu et al., 2017). The second section entails the neuroplasticity theory of depression in explaining how antidepressants and CBT can reverse depression by elevating

the concentration of neurotrophic factors such as Brain-Derived Neurotrophic Factor (BDNF) and promoting positive neuroplasticity in the PFC and hippocampus (Liu et al., 2017). The third section examines the efficacy of combining antidepressants and CBT, and how CBT can help reduce relapses in depression caused by hyperactivity of the amygdala (Arnau-Soler et al., 2016). Finally, the last section presents recommendations for future studies, such as advancing the correlation between genetics and depression; the molecular mechanisms involved in depression; and treatment approaches utilizing precision medicine for clinical use.

INTRODUCTION

According to the American Psychiatric Association (APA), "depression is a medical illness that negatively affects how you feel, the way you think and how you act" (American Psychiatric Association [APA], 2013). Depression is a complex disorder influenced by biological, psychological, and environmental factors (Santarelli et al., 2016). Depression is one of the most common forms of mental illness worldwide (WHO, 2016), yet the pathogenesis of depression and the mechanism of how antidepressants reverse depression are still unclear (Liu et al., 2017). Historically, the medical community has propagated the monoamine (serotonin [5-HT], norepinephrine [NE], and dopamine [DA]) hypothesis as the prevailing explanation of the pathogenesis of depression and antidepressants' targets of monoamine receptors and transporters.

The monoamine hypothesis incompletely postulates that depression is due to a 5-HT, NE, or DA deficiency. Therefore, antidepressants resolve the deficiency by inhibiting the neurotransmitters' reuptake in the synaptic cleft or other methods of limiting their clearance, thus alleviating depressive symptoms. An increase in 5-HT, NE, or DA in the synaptic cleft does not efficiently explain the efficacy of antidepressants (Liu et al., 2017). There are three reasons why the monoamine hypothesis fails to explain the efficacy of antidepressants. First, the delayed onset (~2 weeks) of the effects from antidepressants is inconsistent with the more immediate increase in 5-HT concentration in the synaptic cleft. Second, lowering the concentration of 5-HT in the synaptic cleft via acute tryptophan depletion or serotonin transporter (SERT) enhancer has failed to induce depression in healthy adults. Third, researchers have shown genetic variants associated with an increase in SERT function (*l* allele of 5-HTTLPR) are correlated with a

reduction in depression, and variants associated with a decrease in SERT function (*s* allele of 5-HTTLPR) are correlated with an increase in depression (Liu et al., 2017).

Newer paradigms have emerged attempting to identify and explain what is referred to as the "final common pathway" (Liu et al., 2017), which underlies the pathogenesis or vulnerability to depression, and antidepressants' efficacious effects in reversing or repairing the alteration of this "final common pathway." Researchers have made great strides in correlating the neurobiological effects of stress on the brain leading to depression; and have provided insights into the "final common pathway" of depression and its reversal by antidepressants and Cognitive Behavior Therapy (CBT) (Liu et al., 2017).

BACKGROUND

Pathogenesis of Depression (Stress Model of Depression)

The stress model of depression describes the relationship between stress and depression, exploring how the gene X environment interaction influences the hypothalamic-pituitary-adrenal (HPA) axis in creating negative neuroplasticity (Liu et al., 2017). Neuroplasticity refers to the neural system's ability to adapt to stimuli and respond proficiently to future stimuli by forming and reorganizing synaptic connections (Liu et al., 2017). Gene X environment refers to how different genotypes are affected by the same environment, thus influencing their vulnerability to disease (Lopizzo et al., 2017). Depression is a multifactorial and polygenic disorder where multiple and partially overlapping sets of genes interact with each other and with the environment (Lopizzo et al., 2017). The interplay between environmental factors (such as a stressful life event [SLE]) and an individual's genetics mediating and adapting to stress can dictate susceptibility to depression. Within the gene X environment interaction framework, stress

is the initiator and catalyst in promoting negative neuroplasticity. Negative neuroplasticity occurs when an individual with a maladaptive stress response to an SLE triggers a cascade of neurotoxic events. The dysregulation of the HPA axis creates a hypercortisolemic environment that exerts neurotoxic effects on hippocampal neurons through the glucocorticoid receptors (GR), resulting in decreased neurogenesis, synaptogenesis, and dendritic spines, and an increase in apoptosis of neurons (Liu et al., 2017). Furthermore, chronic stress increases glutamate release in the hippocampus and prefrontal cortex (PFC) and decreases serotonin and dopamine neurotransmission. Stress also influences the decrease in neuronal cell proliferation and promotes apoptosis of glial cells responsible for the clearance of glutamate in the brain. In a vicious cycle, chronic stress continues to exasperate the ill-adaptive stress response promoting negative neuroplasticity in the brain (Liu et al., 2017). The pathogenesis of depression can be assessed through the lens of the chronic stress model of depression and an examination into how antidepressants and CBT can reverse negative neuroplasticity caused by stress.

Neuroplasticity of Depression and Antidepressants

Neuroplasticity has a morphological and a functional component. Furthermore, within the scope of neuroplasticity exists metaplasticity, defined as "activity-dependent and persistent change in neural state that shapes the direction, duration, or magnitude of future synaptic change" (Liu et al., 2017). Metaplasticity is sensitive to both positive environmental cues and negative environmental cues (such as stress).

According to the neuroplasticity theory of depression (Liu et al., 2017), antidepressants can reverse the maladaptive circuitry by: (a) stimulation of postsynaptic monoamine receptors; (b) regulation of presynaptic glutamate, specifically in the PFC; (c) stimulation of AMPA and inactivation of NMDA receptors thus enhancing expression of Brain-Derived Neurotrophic

Factor (BDNF); (d) potentiation of synaptogenesis in the hippocampus, suppressed by stress; and (e) antidepressant may also improve neurogenesis in the hippocampus through activation of the 5-HT_{1A} receptor (Liu et al., 2017). The neuroplasticity theory of depression is supported by evidence of decreased neuroplasticity in the hippocampus and PFC; decreased concentration of BDNF; and antidepressants increasing the concentration of BDNF and improving neuroplasticity in the hippocampus and PFC (Liu et al., 2017). The increase in BDNF promoting neurogenesis in the hippocampus and PFC also promotes neurogenesis in the amygdala, Ventral Tegmental Area (VTA), and Nucleus Accumbens (NAc) (Liu et al., 2017). The increase in neurogenesis in the amygdala exasperates depressive-like symptoms and is a primary reason for relapse (Hayley et al., 2013). In most individuals with depression, CBT can help counter the amygdala's elevated activation if antidepressants alone are not sufficient (Arnau-Soler et al., 2016).

Neuroplasticity and Cognitive Behavior Therapy (CBT)

CBT is a form of psychological treatment that challenges and modifies beliefs, behaviors, and feelings (Corey, 2016). CBT is rooted in principles denoted by a collaborative relationship; a focus on the present; an active and directive stance by the therapist; a psychoeducational approach; and a focus on cognition influencing psychological distress. The goal of CBT is to help individuals recognize negative beliefs and change cognitive perceptions of their environment. A function of the PFC is to regulate cognitive control by processing stimuli and responding appropriately. Cognitive dysfunction observed in an individual with depression is predominantly due to hypoconnectivity of the frontoparietal networks leading to deficits in processing stimuli, reduced attention, concentration, and executive function (Andrade et al., 2010). CBT can improve network connectivity seen in depression by increasing the functional network connectivity between the PFC and amygdala. Researchers have shown that CBT can

improve an individual's mood, creating a positive effect by increasing activity in the dorsolateral and dorsomedial PFC, and minimizing activity in the amygdala (Uscinska et al., 2019).

Antidepressants and CBT

Depression is a complex disorder that requires a treatment plan specific to each individual (Roiser et al., 2012). Antidepressants are pharmacologically beneficial but have a ceiling of efficacy. Antidepressant-induced neuroplasticity will not permanently reverse the negative neuroplasticity in the PFC and hippocampus caused by stress. The vulnerability and maladaptive response to an SLE will continue to persist. Stress is a constant enabler, and thus individuals living with depression may need continuous maintenance of antidepressant therapy (Andrade et al., 2010). Therefore, the combination of an antidepressant and CBT is the best approach to treating depression. Both antidepressants and CBT are efficacious in treating depression, but their therapeutic effects are achieved in different ways. Antidepressants' effects (Uscinska et al., 2019) consist of a "bottom-up" approach; in comparison, CBT's effects consist of a "top-down" approach. Importantly, there is a favorable window at the start of antidepressant therapy for imprinting healthy cognitions and behaviors, establishing healthy neurocircuitry. Implementing treatment outside of this therapeutic window will increase the chance of antidepressant refractoriness (Andrade et al., 2010). Additionally, an individual's environment, genetics, and epigenetics may impact treatment resistance.

RESEARCH STRATEGIES

A comprehensive literature search was performed using PubMed and Google Scholar databases to retrieve original articles that evaluated research relating to the topic of neuroplasticity of depression and how antidepressants and CBT reverse the effects of depression. The literature analysis included a review of published literature from diverse disciplines (Clinical Neurology, Psychology, Neuropharmacology, Neurophysiology, and Radiology) and a range of interdisciplinary research and clinical method strategies (molecular and genetics, imaging/functional study modalities, and clinical research). More specifically, the published literature included basic, translational and clinical research.

DISCUSSION

PART I

Pathogenesis of Depression

Newer paradigms have emerged attempting to identify and explain what is referred to as the "final common pathway" (Liu et al., 2017), which underlies the pathogenesis or vulnerability to depression, and antidepressants' efficacious effects in reversing or repairing the alteration of this "final common pathway." It is well understood that a primary symptom of depression is a loss of interest (anhedonia) (Stone et al. 2008). Anhedonia in depression is the product of a "final common pathway" or common final neural state. The neural network that mediates positively motivated behavior involves the interplay between the dorsal (positive motivation) brain regions (PFC, parietal and temporal cortices, limbic, hypothalamus [lateral], and thalamus), that regulate the ventral (stress regions) brain regions (amygdala, subgenual anterior cingulate cortex [sgACC)], hypothalamus [paraventricular nuclei], ventral striatum, and bed nucleus of the stria

terminalis [BNST]) (Stone et al. 2008). The Mayberg model, via neuroimaging studies, support the premise of an interplay between the dorsal (positive motivation regions) and ventral (stress regions) in the development of the symptoms of depression (Stone et al. 2008). The Mayberg model states that a shift in neuronal activity favors the ventral (stress) regions in individuals with depression (Stone et al. 2008).

What is the pathogenesis of depression? Short answer: depression is a multifactorial and polygenic disorder where multiple and partially overlapping sets of genes interact with each other and the environment (Lopizzo et al., 2017). Current research postulates multiple factors such as HPA axis dysfunctions, neuroimmune responses, neurodegenerative alterations, circadian rhythms, genetics, and epigenetics play a role in the pathology of depression (Massart et al., 2012). The common denominators underlying all of the mentioned etiologies are stress and genetics. All of the above factors play a role in the complexities of depression, but stress is central in the pathogenesis of depression. This review's focus is not to discuss all current research (theories) on the pathogenesis of depression but to explore one of the primary contributors, namely the stress (chronic) model of depression. Of note, chronic stress is defined by the HPA axis response and other systems that participate in physiological adaptation (e.g., autonomic nervous system, immune system, brain behavioral prioritization, among others) (Herman et al., 2016).

The various biological systems encompassing all organisms can maintain homeostasis or a dynamic equilibrium (de Kloet et al., 2005). The dynamic equilibrium can be disturbed by physiological and psychological events known as 'stressors' (de Kloet et al., 2005). In accordance, organisms are constantly monitoring and appraising stressors toward the pursuit of maintaining dynamic equilibrium. The appraisal of incoming stimuli includes referencing

previous cognitive experiences and procuring an appropriate response. If a reference point does not exist, the response increases alertness, vigilance, and cognitive processing. The interplay between incoming sensory information and the appraisal process involves the hippocampus, PFC, and amygdala (de Kloet et al., 2005).

Stress is divided into two responses, acute stress response and chronic stress response (de Kloet et al., 2005). The general adaptive syndrome (GAS) illustrates the model of acute stress, consisting of three stages: alarm, resistance, and exhaustion. The alarm stage consists of perceiving a threat or stressor; the resistance stage consists of a physiological response, regulated by the sympathetic nervous system; and the exhaustion stage, which consists of depleting bodily resources due to prolonged stress when appropriate coping mechanisms fail to contain the stressor. The normal stress response is termed "allostasis," entailing an effective coping mechanism to a stressful event that incudes rapid activation and proper termination. If a maladaptive or an inadequate stress response occurs, it is referred to as an allostatic load and is deemed chronic (de Kloet et al., 2005). It is understood that stress influences neurogenesis; reciprocally, neurogenesis influences the stress response (Egeland et al., 2015). This review focuses on the latter, chronic stress and its pathology.

Hypothalamic-Pituitary-Adrenocortical Axis (HPA) Axis

When a stressful event is detected by the brain via limbic pathways and ascending brain pathways from sensory and visceral stimuli, the adapted physiological response functions in two modes: fast and slow (de Kloet et al., 2005). The fast mode begins with the hypothalamic release of Corticotropin-Releasing Hormone (CRH) and activation of the sympathetic, "fight or flight" response. The sympathetic response (secretion of CRH) is regulated by the CRH1 receptor (CRHR1). CRHR1 also activates the HPA axis. In turn, the secretion of both CRH and arginine

vasopressin (AVP) from the paraventricular nucleus (PVN) of the hypothalamus by parvocellular neurons occurs. The parvocellular neurons secrete CRH and vasopressin and activate pro-opiomelanocortin (POMC) synthesis in the anterior pituitary, leading to secretion of adrenocorticotropin hormone (ACTH). ACTH stimulates the release of corticosteroids (cortisol) in the adrenal cortex. Corticosteroids circulate throughout the body for the function of stress, recovery, and adaptation. The receptor system encompassing MR (mineralocorticoid receptor) and GR (glucocorticoid receptor) binds to the same corticosteroid, cortisol. The release of corticosteroids by the adrenal cortex is involved in both modes of stress response and is regulated by MR and GR. MR and GR are complementary to each other in the management of the stress response. MR predominately is tasked with predictability, appraisal and risk management, reactivity, flexibility, and the onset of the stress reaction. GR functions are controllability, memory storage, adaptation, and terminating the stress reaction. The binary receptor system coordinates an efficient and effective stress response (de kloet, 2013). The HPA axis is regulated by a negative-feedback loop utilizing cortisol in the regulation of CRH and AVP secretion by activating GRs in the hippocampus and paraventricular nucleus neurons in the hypothalamus.

The hyperactivity of the HPA axis is due to the dysregulation of GRs. The hippocampus and its inhibitory regulation of the HPA axis are compromised, in turn, increasing the circulating corticosteroid levels, leading to more detrimental hippocampal dysfunction (Massart et al., 2012). A hypercortisolemic environment creates a vicious cycle due to chronic stress (Holsboer, 2000). However, the corticosteroid signaling cascade is complex and involves various transcription factors, chaperones, proteins, and regulatory mechanisms that mediate MR and GR actions complicating matters even more in pathology (de Kloet et al., 2005). Nonetheless, an

imbalance in the MR:GR ratio has been detected in depressed patients (de Kloet et al., 2005). Research (Vose et al., 2017) has shown that chronic stress in rodents can change the amount of corticosterone (cortisol equivalent) and ACTH released and altering MR and GR's sensitivity in the hippocampus, PFC, and other brain areas.

Genetic Considerations

The combination of a stressful life event (SLE) and genetic susceptibility can have a detrimental impact on the MR and GR signaling mechanism, thus creating a vulnerable phenotype (de Kloet et al., 2005). An individual's vulnerability to depression is defined at three levels: clinical phenotype (psychological - emotional reactivity); functional phenotype (physiological – neuroendocrine reactivity); and genotype (genetics – i.e., polymorphisms in GR gene). Particular genetic backgrounds have been shown to increase susceptibility to depression, such as polymorphisms in the GR or FKBP5 gene, both implicated in HPA axis hyperactivity. Conversely, particular genetic backgrounds have been shown to increase resiliency in developing depression, such as a polymorphism in the ER22/23 EK allele of the GR gene. An individual with the resiliency polymorphism exhibits healthier cognitive function than the general population and better treatment outcomes if they develop depression. Other polymorphisms of the GR gene have also been implicated in dysfunctional regulation of HPA response to stress (de Kloet et al., 2005).

In 2020, Belzeaux et al. published a study identifying the G protein-coupled receptor (GPR56) encoded by ADGRG1 gene, as a possible biomarker for depression and antidepressant efficacy (Belzeaux et al., 2020). The study indicated downregulation of GPR56 in the PFC is correlated to depressive behavior. Furthermore, chronic stress induces the downregulation of GPR56 and antidepressants can reverse the negative effects (Belzeaux et al., 2020).

Chronic Stress Effects on Neuroplasticity

Hippocampus

Prolonged corticosteroid exposure has been implicated in negative neuroplasticity in the hippocampus, causing a reduction in neurogenesis and impairment of synaptic plasticity Pittenger et al., 2008). The morphological changes caused by chronic stress include atrophy of apical dendritic spines and branches of the pyramidal neurons in the CA3 (cornu ammonis) and suppression of new granule neurons in the dentate gyrus (DG) (Pittenger et al., 2008). These long-term effects of chronic corticosteroid elevation in the hippocampus have been hypothesized to occur via epigenetic mechanisms (i.e., DNA methylation and histone modification) in the HPA axis (Pittenger et al., 2008). Elevated levels of corticosteroids target genes that encode structural proteins changing dendritic morphology, in turn altering the length of the tree, as well as alterations in the glutamate-induced voltage shift in the soma (de Kloet et al., 2005). Glutamate, the primary neurotransmitter in the brain, is highly influenced by overactive corticosteroid levels, increasing NMDA (glutamate) receptor activity leading to dysfunction in glutamate signaling and potentially leading to excitotoxicity in the cells (de Kloet et al., 2005).

Another hippocampal area affected by chronic stress and elevated corticosteroid levels is the dentate subgranular zone and the reduced activity in the proliferation of its progenitor cells. Chronically elevated corticosteroid levels hinder proliferation in the dentate subgranular zone, but a partial reversal is possible with treatment (Pittenger et al., 2008).

Long-term Potentiation and Long-term Depression in the Hippocampus

Long-term potentiation (LTP) in the hippocampus is the persistent stimulation of afferent fibers leading to synaptic plasticity via NMDA (glutamate) receptors and the induction of learning and memory (Pittenger et al., 2008). Long-term depression (LTD) is the counterbalance

of LTP and functions to prevent the saturation of hippocampal synapses by decreasing synaptic strength (NMDA receptors) using low-frequency stimulation of afferent fibers. In depression, the imbalance between LTP and LTD is tipped in favor of LTD (Pittenger et al., 2008). Elevated corticosteroid levels impair hippocampal neurogenesis. Low corticosteroid levels amplify long-term potentiation (LTP) due to preferential activation of MRs in the hippocampus. Conversely, high corticosteroid levels mitigate LTP due to saturated MRs in the hippocampus, leading to activation of GRs (de Kloet et al., 2005).

Prefrontal Cortex

Chronic stress affects the PFC, specifically medial PFC (mPFC), similarly to the hippocampus. Chronic stress reduces the induction of LTP within the PFC and induces atrophy of the apical dendrites of pyramidal cells in the mPFC (Pittenger et al., 2008). Chronic stress minimizes the excitatory pathways projecting to the PFC, leading to PFC hypoactivity in depression. Conversely, in depression, the amygdala is hypertrophic and hyperactive, thus enhancing the projections from the ventromedial PFC (vmPFC) to the amygdala (Pittenger et al., 2008). The projections between the PFC, hippocampus, and amygdala are complex but described here in simple terms: chronic stress minimizes LTP induction in the hippocampal-PFC and basolateral amygdala-PFC synapses, but the connection, going from PFC to the basolateral amygdala, experiences an upregulation in LTP induction (Vose et al., 2017). The mPFC is compromised in depression, thus decreasing its ability to effectively communicate with the hippocampus and mediate adverse behavior (Kim et al., 2015).

Amygdala: Stress-Induced Hypertrophy

Chronic stress enhances hypertrophy in the amygdala, possibly due to increased neurocircuitry activation that controls fear memories, emotion, and anxiety (Pittenger et al.,

2008). The sites of neurogenesis in the amygdala are regionally specific. According to Pittenger et al. (2008), “Stress induces increased neuroplasticity (synaptogenesis, elongation of dendritic spines, and dendritic spine density) in the basolateral amygdala principal cells and in the bed nucleus of the stria terminalis (BNST), a projected target of the amygdala” (Pittenger et al., 2008). Increased LTP in the basolateral amygdala leads to increased fear learning and anxiety. Interestingly, in the central amygdala, chronic stress has delayed neurogenesis (induction of LTP and dendritic arborization), which has been an area of focus for reversing the effects in the basolateral amygdala and hippocampus (Vose et al., 2017). The lateral amygdala (LA) is also implicated in the stress-induced increase in LTP (Suvrathan et al., 2014). Chronic stress promotes greater neural excitability and reduced GABAergic regulation; the increased excitability results in the upregulation of NMDARs (glutamate) and an increase in LTP (Suvrathan et al., 2014).

Contributions of Glutamate to Neuronal Atrophy After Stress

It is understood that hyperactive glutamate release can cause excitotoxicity and potentially lead to cell death (Sanacora et al., 2012). Glutamate, the brain's primary neurotransmitter, far outnumbers other neurotransmitters in the brain, except for GABA (Sanacora et al., 2012). Glutamatergic synapses in the brain are tripartite (presynaptic, postsynaptic, astrocytic glia cells). Astrocytes are necessary for the reuptake of glutamate in the synaptic cleft. Astrocytic glial cell dysfunction (low ratio of glia to neurons) plays a role in the pathology of depression (Vose et al., 2017).

The primary brain structures associated with depression, such as PFC, hippocampus, and amygdala, communicate via glutamatergic signaling (Vose et al., 2017). Acute stress increases extracellular glutamate in the PFC, and excess glucocorticoid levels increase glutamate secretion

in the CA1 of the hippocampus. Chronic stress increases extracellular glutamate in the CA3 region of the hippocampus. Chronic stress-induced increases in the extra-synaptic sites disturb the balance between synaptic and extra-synaptic NMDA (glutamate) receptors creating excitotoxicity and neurodegeneration (Pittenger et al., 2008). The effects of chronic stress on reducing postsynaptic ionotropic glutamate receptors (GluN2B and GluA2/GluA3) in the PFC have been proposed as a mechanism underlying the dysregulation of fear extinction (Sanacora et al., 2012).

Glial Cells (Astrocytes)

Glial cells in the brain, specifically astrocytes, have the role of regulating K+ and glutamate in determining excitability levels of neurons and neurotransmitter metabolism (Rial et al., 2015). Glial cells regulate the synaptic levels of glutamate that augment NMDA and AMPA receptors' density on the postsynaptic membrane influencing synaptic plasticity (Rial et al., 2015). Glial cells' regulatory mechanism involves Excitatory Amino Acid Transporters 1 and 2 (EAAT1 and EAAT2), which are astroglia glutamate transporters that function to prevent excess excitability and potential spillover into the extra-synaptic space, thus mitigating glutamate excitotoxicity (Sanacora et al., 2012). Chronic stress has been shown to decrease the proliferation of glial progenitor cells (Sanacora et al., 2012). One of the glial cells' roles is in neurotransmitters' metabolism, specifically, converting glutamate into glutamine, a precursor for GABA (inhibitory neurotransmitter in the brain). GABA plays a significant role in the continual maintenance of neuronal homeostasis (Sanacora et al., 2012). In depression, there is a dysregulation in the frontolimbic region where astrocytes have lost the ability to regulate synaptic levels of K+ and clearance of extracellular glutamate, resulting in increased excitability and an imbalance of NMDA to AMPA receptors.

PART II

Neuroplasticity of Depression and Antidepressants (Structural and Functional Changes)

As previously defined in the background section, neuroplasticity refers to the neural system's ability to adapt to stimuli and respond proficiently to future stimuli by forming and reorganizing synaptic connections (Liu et al., 2017). Neuroplasticity has a morphological and functional component. Furthermore, within the scope of neuroplasticity exists metaplasticity, defined as "activity-dependent and persistent change in neural state that shapes the direction, duration, or magnitude of future synaptic change" (Liu et al., 2017). Metaplasticity is sensitive to both positive environmental cues and negative environmental cues (such as stress). Researchers have shown that the brain is more plastic than previously thought. Furthermore, the brain contains stem cells that can differentiate into neuronal or glial cells, thus contributing to the neuroplasticity of pharmacotherapy (antidepressants) and psychotherapy (CBT) treatments (Higgins et al., 2019).

Neuroplasticity of Antidepressants – Early Changes

The initial neuroplasticity changes are facilitated by glutamate binding to the postsynaptic NMDAR (ionotropic glutamate receptor). The NMDAR cascade, in this case, activates lipid-signaling pathways (arachidonic acid, platelet-activating factors, prostanoid, among others) in a positive-feedback regulation. NMDAR activation also initiates calcium calmodulin-dependent kinase II (CaMKII) and increases AMPARs (ionotropic glutamate receptor). The glutamatergic cascade results in long-term potentiation (LTP) and synaptic strengthening (Andrade et al., 2010).

Neuroplasticity of Antidepressants – Long-Term Changes

"Long-term changes involve the induction of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) that act on tyrosine kinase (Trk) receptors to activate intracellular cascades such as cAMP-PKA, CaMKII, mitogen-activated intracellular kinase (MAPK), among others" (Andrade et al., 2010). These signaling molecules, in turn, activate various transcription factors, most importantly, cAMP response element-binding protein (CREB). CREB, in turn, activates the synthesis of proteins and enzymes (BDNF, VEGF, etc.) involved in the cytoarchitecture of neuroplasticity (Andrade et al., 2010). The end products of the intracellular signaling cascades are neurogenesis (synaptogenesis, dendritic branching, etc.) and increased glial cells in the hippocampus (predominantly, dentate gyrus), PFC, and amygdala (Andrade et al., 2010) - consistent with the timeline of antidepressants.

Antidepressants Can Reverse the Maladaptive Circuitry By:

1. **Stimulation of postsynaptic monoamine receptors**

Antidepressants can promote positive neuroplasticity by stimulation through postsynaptic monoamine receptors. Generally, G-protein coupled receptors (GPCR) initiate an intracellular cascade consisting of the activation of adenylate cyclase (AC), which catalyzes ATP to cyclic adenosine monophosphate (cAMP), which activates cAMP response-element binding protein (CREB) via protein kinase A (PKA) (Carlezon et al., 2005). CREB is the transcription factor responsible for gene expression of many of the proteins (BDNF, GluR1, among others) involved in neurogenesis in the hippocampus and other areas in the brain. The atrophy in the hippocampus and PFC created by chronic stress can be reversed by increasing neurogenesis in these areas; one of the many ways is to increase postsynaptic monoamine receptors (Carlezon et al., 2005).

CREB

CREB is expressed in all cells of the brain. CREB resides in the nucleus functioning as a transcription factor, specifically stimulus-transcription coupling (cell membrane events into gene expression). CREB is predominantly responsible for the expression of most neuronal proteins, thus wielding tremendous influence over individual neurons and neuronal circuits (Carlezon et al., 2005). In the hippocampus, the increase in CREB activity plays an instrumental role in the efficacy of antidepressants (selective serotonin-reuptake inhibitors [SSRI] and Serotonin-norepinephrine reuptake inhibitors [SNRI]). CREB promotes the expression of one of its target genes, BDNF. BDNF, a growth factor, stimulates neurogenesis and dendritic arborization. Hippocampal neurogenesis helps regenerate the negative neuroplasticity caused by chronic stress and restores normal mood (Carlezon et al., 2005). Such processes are aligned with the timeline of antidepressants' efficacy (Carlezon et al., 2005).

With respect to dynamic equilibrium, high expression of CREB has its disadvantages. Increases in CREB in the hippocampus produce antidepressant effects. Conversely, a similar increase in CREB in the nucleus accumbens (NAc) produces depressive-like symptoms due to increased dynorphins and stimulation of K opioid receptors. Therefore, CREB can have adaptive and maladaptive effects depending on the brain structure. Thus, extreme increases or decreases in CREB activity can be detrimental. Furthermore, standalone CREB therapeutics as antidepressants have had difficulty gaining traction because of the brain's global expression (Carlezon et al., 2005).

2. Regulation of presynaptic glutamate, specifically in the PFC

Antidepressants regulate presynaptic glutamate secretion by a mechanism illustrated in a study (Sanacora et al., 2012) using the synaptosome superfusion technique over a two-week

period, which reduced depolarization-evoked release of glutamate. Chronic treatment of antidepressants creates an adaption that changed the protein-protein interactions involved in the presynaptic SNARE (soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor) protein complex (formed by synaptobrevin-2, syntaxin-1, and SNAP-25) that regulates fusion of presynaptic vesicles with the presynaptic membrane (Sanacora et al., 2012). This process (Sanacora et al., 2012) entails the phosphorylation of CaMKII (high concentration at synapses), resulting in the reduced binding of syntaxin-1 to CaMKII and increased binding to Munc-18 (protein in synaptic vesicles fusion and exocytosis). In turn, syntaxin-1 and the SNARE complex interaction are reduced, resulting in a decrease in the depolarization-evoked release of glutamate (Sanacora et al., 2012). The reduction in glutamate release helps reduce neurotoxic effects caused by glutamate excitotoxicity, thus promoting an environment for neurogenesis, synaptogenesis, and neurocircuitry (Liu et al., 2017).

3. Stimulation of AMPA and inactivation of NMDA receptors, thus enhancing expression of Brain-Derived Neurotrophic Factor (BDNF)

BDNF

Brain-derived neurotrophic factor (BDNF) is broadly expressed throughout the brain regions but with higher densities in the dentate gyrus (DG) and the subventricular zone (SVN) structures (Miao et al., 2020). BDNF's role is to regulate neurogenesis and neuronal maintenance. BDNF has two primary target receptors, tropomyosin receptor kinase B (TrkB) and p75 receptor ($p75^{NTR}$). BDNF is secreted by neuronal cells, crosses the blood-brain barrier (BBB), and is regulated by CREB, as previously mentioned. Research (Miranda et al., 2019) has shown that BDNF contributes to regulating the remodeling of 5-HT neuronal terminals in the cortical regions. Furthermore, additional studies (Miranda et al., 2019) have shown that serum BDNF

(sBDNF) is lower in individuals with depression. One of the antidepressants' effects is to increase BDNF expression in the hippocampus, promoting neurogenesis and dendritic arborization (Carlezon et al., 2005).

BDNF polymorphisms (such as val66met) have been implicated in decreased BDNF leading to reduced hippocampal functioning (Pittenger et al., 2007). Epigenetic modulations such as DNA methylation and histone modification have also contributed to the inhibition of various *Bdnf* gene variants and their expression, leading to the reduction of BDNF (Miao et al., 2020). For example, chronic stress has been implicated in the DNA methylation at the *Bdnf* exon IV promoter region, thus reducing BDNF expression in the hippocampus (Miao et al., 2020).

Stimulation of AMPA and inactivation of NMDA receptors

Antidepressants such as Ketamine (non-competitive NMDA antagonist) exhibit a different therapeutic mechanism of action than other antidepressants (monoaminergic antidepressants). Ketamine increases the release of presynaptic glutamate (Du et al., 2006). The increased glutamate release preferentially favors AMPARs over NMDARs due to Ketamine's blockade of NMDARs (Du et al., 2006). In turn, this results in upregulation of AMPARs (GluR1, among others) and an increase in intracellular signaling cascades that promotes increased expression of BDNF and increased exocytosis of BDNF by increasing Ca^{2+} in the cytoplasm. The extracellular BDNF will stimulate its membrane receptor TrkB resulting in increased gene expression and increased neuroplasticity (Liu et al., 2017). Ketamine's effects are experienced faster than monoaminergic antidepressants' (~2 weeks) effects because Ketamine only requires protein translation but not transcription resulting in a faster synthesis of BDNF, thus increasing neurogenesis. The translation of BDNF via ketamine mechanism of action, is due to the regulation of eukaryotic elongation factor 2 kinase (eEF2K) that phosphorylates eEK2 by the

inhibition of NMDAR, which leads to inhibition of eEF2K and dephosphorylation of eEF2 and increasing translation and BDNF synthesis (Monteggia et al., 2103). Monoaminergic antidepressants, indirectly increase AMPAR expression but after a series of downstream signaling cascades at a more gradual rate (Monteggia et al., 2103).

Although the increase in presynaptic glutamate release yielding antidepressant effects may seem contradictory at first, the glutamate receptor family is complex and diverse. Furthermore, an alternative explanation of whether an increase in glutamate is "good" or "bad" is referred to as the "NMDAR paradox" (Hardingham et al., 2010). The NMDAR paradox states that it is the location of NMDARs that determines a neuroprotective or neurotoxic glutamatergic signal. Accordingly, synaptic NMDARs exhibit neuroprotective behavior in contrast to extra-synaptic NMDARs that exhibit neurotoxic behavior (Hardingham et al., 2010). Furthermore, this concept illustrates that synaptic Ca^{2+} overload is not the predominant reason for excitotoxicity, but instead, it is the Ca^{2+} overflow to the NMDARs in the extra-synaptic region that is implicated in neurotoxicity (Hardingham et al., 2010).

4. Potentiation of synaptogenesis in the hippocampus, suppressed by stress

Antidepressants have been shown to increase LTP in the dentate gyrus by increased stimulation of the perforant pathway to granule cells. One study stated, "SSRI (fluoxetine) administration increases baseline field potentials in the dentate gyrus" (Pittenger et al., 2007). The increase in neuroplasticity in the dentate gyrus may be due to newborn granule cells that exhibit greater plasticity potential. Furthermore, Hayley et al. (2013) state that approximately a third of hippocampal neurons can be exchanged during a lifespan (Hayley et al., 2013). Also, chronic antidepressant treatments can block the stress-induced inhibition of LTP and prevent

LTD in the CA1 region of the hippocampus (Pittenger et al., 2007). The result is an increase in neurogenesis and synaptic connectivity via LTP processes (Liu et al., 2017).

5. **Antidepressant may also improve neurogenesis in the hippocampus through activation of the 5-HT_{1A} receptor**

5-HT_{1A} receptors play an essential role in the mechanism of action of antidepressants. 5-HT neurons are predominantly located in two brain regions: raphe nuclei (presynaptic auto-receptors) and postsynaptic neurons of 5-HT nerve terminals in the cortico-limbic regions. 5-HT_{1A} receptors are located in the somatodendritic region and respond to local serotonin by increasing potassium conductance; hyperpolarizing the neuronal membrane; and inhibiting serotonergic firing pyramidal neurons in the hippocampus and cortex regions. This mechanism helps to desensitize the 5-HT_{1A} receptor first and then to await recovery. The postsynaptic 5-HT_{1A} receptors in the cortico-limbic regions do not desensitize or are downregulated in the process. Thus, the net effect is increased serotonin release over time (Gray et al., 2013). The hippocampus receives a high density of 5-HT innervation fibers from the raphe nucleus; thus, 5-HT mediated neurotransmission increases neurogenesis in the hippocampus. Furthermore, specific 5-HT receptor subtypes such as 5-HT_4 cause mature granule cells in the dentate gyrus to curb calbindin (Ca^{2+} binding protein) expression and begin to express characteristics of immature granule cells (Mahar et al., 2014).

Negative Neuroplasticity in the Amygdala, VTA, and NAc

The increase in BDNF promoting neurogenesis in the hippocampus and PFC also promotes neurogenesis in the amygdala, Ventral Tegmental Area (VTA), and Nucleus Accumbens (NAc) (Liu et al., 2017). The increase in neurogenesis in the amygdala exasperates depressive-like symptoms and is a focal reason for relapse (Hayley et al., 2013). In most

individuals with depression, CBT can help counter the amygdala's elevated activation if antidepressants alone are not sufficient (Arnau-Soler et al., 2016).

The increase in BDNF does promote neurogenesis, but the effects are structure-dependent (Hayley et al., 2013). For example, the increased expression of BDNF in the amygdala, VTA, and NAc promotes neurogenesis, dendritic arborization, and synaptogenesis, but the effects are "negative neuroplasticity." Increased plasticity in the amygdaloid nuclei increases susceptibility to depression by augmenting the fear response. Although BDNF in the amygdala is a requisite for fear learning, excess enhancement of the fear response can promote pathology. This phenomenon is observed in individuals with depression in remission yet display heightened arousal and vigilance; even benign stressors could trigger a possible relapse if not managed immediately (Hayley et al. 2013). The importance and effects of combining pharmacotherapy with psychotherapy (CBT) can demonstrate its value in minimizing potential relapse and exhibiting synergistic effects (discussed in subsequent sections).

PART III

Neuroplasticity and Cognitive Behavior Therapy (CBT)

As mentioned earlier in this review, neuroplasticity is the brain's ability to adapt and change by constant remodeling of synaptic connections and neurogenesis. Long-term potentiation and synaptic plasticity that are strengthened by repetitive firing are the basis for learning and memory. Based on Hebbian theory, “neurons that fire together, wire together” and “neurons that fire apart, wire apart” (Keysers et al., 2014). Furthermore, studies have shown that learning in concert with new interneuron connections leads to neurogenesis (Gould et al., 1999). The greater the redundancy in a specific behavior, the greater the anatomical and functional adaption to the repetitive stimuli (Jones, 2000). Of note, the outcome of an incoming experience

depends on the duration, timing, and intensity of the stimuli (Gunnar et al., 2006). Studies (Månsson et al., 2016) have shown that fear and anxiety increase the recruitment of neurons in the amygdala and the neuronal response to anxious behavior. A study (Månsson et al., 2016) displayed increased dendritic spine density after fear conditioning. Yet, negative neuroplasticity was reversed during fear extinction (Månsson et al., 2016).

Cognitive behavior therapy (CBT) is fundamentally rooted in two ideologies: (a) that all behavior, adaptative or maladaptive, is learned; (b) cognitive distortions and faulty thinking give rise to psychological disorders. CBT theorists postulate that learning exists on an ever-changing continuum and that dysfunctional behavior that has been learned can be unlearned and replaced with functional behavior. CBT is a psychotherapeutic treatment that challenges and modifies beliefs, feelings, and behaviors (Corey, 2016). The underlying logic in CBT is that experience-dependent learning follows the principles of neuroplasticity. Since CBT is a learning-based therapy, then it is logically sound to infer the effects of CBT should follow principles of neuroplasticity (Kleim & Jones, 2008). Therefore, faulty thinking or cognitive distortions that have been learned, accordingly, can be unlearned.

CBT utilizes top-down processing (slow, explicit) that is more calculated than bottom-up processing (fast, implicit) (Clark & Beck, 2010). Top-down processing is performed by the orbitofrontal cortex (OFC), ventromedial PFC (vmPFC), and anterior cingulate cortex (ACC), among other subcortical regions and cortex regions that are involved in the regulation of emotions. For example, cognitive restructuring is a CBT technique used to replace faulty thinking with rational thinking, resulting in an appropriate emotional response that curtails negative emotions (Ochsner & Gross, 2007). The regulation of emotions positively results in reduced stimulation of the amygdala and mitigation of neurotoxicity from a hyperactive HPA

axis. In turn, it results in positive neuroplasticity and a healthier mental state (Carlson et al., 2007).

CBT utilizes various techniques that educate an individual on the appraisal component of cognition by proactively assessing and evaluating thoughts and emotions in order to minimize faulty thinking. CBT teaches an individual to view thoughts and emotions with a filter that compartmentalizes thoughts and emotions as short-term, transient mental events (Shimamura, 2000). This process allows an individual to consciously and proactively process thoughts, emotions, and behaviors (Shimamura, 2000). The result is the ability to determine and process thoughts, emotions, and behaviors that are beneficial, rather than automatically reacting to them (Chambers et al., 2009).

Metacognition

Metacognition is defined as "the monitoring and control of cognitive processing" (Shimamura, 2008). The continuous appraisal of incoming stimuli and the respective accompanying emotions (adaptive or maladaptive) create the exhibited behavior and promote negative neuroplasticity and ultimately pathology. Metacognition is mediated by midfrontal brain regions, predominately PFC (extensive top-down control) (Shimamura, 2008). CBT addresses the metacognitive level and incorporates techniques such as mindfulness and other metacognitive therapies (Chambers et al., 2009).

PART IV

Antidepressants and CBT

A poly-treatment approach has been shown to be efficacious in treating depression (Hayley et al., 2013). As mentioned in the background section, both antidepressants and CBT are efficacious in treating depression, but their therapeutic effects are achieved in different ways.

Antidepressants' effects (Uscinska et al., 2019) consist of a "bottom-up" approach; in comparison, CBT's effects consist of a "top-down" approach. The "bottom-up" approach is in reference to a two-step process entailing an incoming stimulus (implicit) that is processed by the limbic system before reaching the cortical regions. The "top-down" approach is a three-step process entailing an incoming stimulus, cognition of the stimulus, and an emotional response to the stimulus. An explanation for the differences in the approaches is that antidepressants predominantly act through the serotonergic system by modulating dorsal raphe nuclei (DRN) and its projections via serotonergic pathways in the subcortical and cortical regions (hippocampus, PFC, amygdala, basal ganglia) utilized in emotional processing (Godlewska et al., 2020). Conversely, CBT strengthens the frontal cortex regions (mPFC and anterior cingulate cortex [ACC]) by reducing negative bias, in turn improving emotional regulation (Hayley et al., 2103). The pregenual anterior cingulate cortex (pgACC) plays an important role in emotional and cognitive processing due to its central anatomical location in the neurocircuitry involved in top-down processing (Godlewska et al., 2020). More broadly, antidepressants (pharmacotherapy) decrease limbic hyperactivity, and CBT (psychotherapy) increases emotional regulation. The goal is to strive for a healthy mental state where the brain structures can maintain a dynamic equilibrium where information that is processed by the amygdala, VTA, and NAc is regulated by cortical structures (PFC) in regulating emotions.

CBT targets cognitive processes implicated in promoting negative schemata and negative bias (top-down effect) (Godlewska et al., 2020). In contrast, antidepressants target the brain structures (limbic system) involved in the formation of negative schemata and negative bias (bottom-up effect) (Godlewska et al., 2020). A study by Goldapple et al. (2004) observed lower relapse rates for patients utilizing CBT alone or with antidepressants (Goldapple et al. 2004).

With that said, this is a simplistic explanation of the complex inner workings of the brain. Both, antidepressants (pharmacotherapy) and CBT (psychotherapy) can have top-down and bottom-up effects, as the neurocircuitry and pathways in the brain can have overlapping effects (Godlewska et al., 2020).

The combination of antidepressant and CBT have shown to result in synergistic effects (Godlewska et al., 2020). Antidepressants, utilizing the bottom-up process, modulate monoamine neurotransmission and begin improving mood by inducing positive neuroplasticity, but this takes time (~2 weeks). During this time, for best results, psychotherapy is recommended, which can immediately improve cognition, resulting in greater emotional regulation that is less taxing on the limbic system. Furthermore, studies have shown that an individual's environment has a tremendous influence on pharmacotherapy's efficacy. Thus, it is paramount that individuals beginning an antidepressant regimen be cognizant of how their environment can affect the antidepressant's efficacy (Godlewska et al., 2020). It is also important to note that without modified changes in top-down regulation via LTP, it will be challenging to induct new behavioral patterns (Fuchs, 2004).

RECOMMENDATIONS FOR FUTURE STUDIES

Future studies can provide evidence to support the correlation between the pathogenesis and the neuroplasticity of depression through several avenues: (a) continued research of how genetics influence the stress response, how genetics impact neuroplasticity in depression, and how genetics influence treatment efficacy; (b) a deeper understanding of the molecular mechanisms, such as intracellular signaling cascades involved in neuroplasticity of depression; and specific neurotransmitter receptor targets involved in the signaling cascades impacting antidepressant efficacy and future antidepressant development (Liu et al., 2017); and (c) a deeper understanding of antidepressants' bottom-up treatment approach compared to psychotherapy's top-down treatment approach.

Currently, the combination of antidepressants and CBT is the preferred treatment method for the greatest efficacy. Advances in the technology for diagnosis and treatment of depression have enabled practitioners to personalize treatments for patients. Precision medicine considers clinical data and individual biomarkers, such as genetics, protein expression, neuroimaging, neurocognitive performance, personality, among other characteristics, to customize an individual's treatment plan (Li et al., 2021). Therefore, precision medicine can serve as a pharmacogenetic guidance approach for depression, increasing the response rate and remission rate of antidepressants and psychotherapy (Li et al., 2021). Precision medicine for depression is a newer approach requiring further studies to better optimize its effectiveness as a treatment approach (Li et al., 2021). Finally, depression is a heterogeneous disorder, and with insufficient knowledge of its etiology and pathophysiology, the disorder's complexity undermines the ability to formulate targeted treatments (Li et al., 2021). In pursuing our deeper understanding of

depression, the future for research and clinical treatment of depression is rich with promising endeavors.

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