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Plasticity-augmented psychotherapy for refractory depressive and anxiety disorders

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ABSTRACT

Psychotherapy and pharmacotherapy have been the mainstays of treatment for depression and anxiety disorders during the last century. However, treatment response has not improved in the last few decades, with only half of all patients responding satisfactorily to typical antidepressants. To fulfill the needs of the remaining patients, new treatments with better efficacy are in demand. The addition of psychotherapy to antidepressant treatment has been shown to be superior to pharmacotherapy alone. However, the time costs of psychotherapy limit its use for clinicians and patients. Advancements in neuroscience have contributed to an improved understanding of the pathogenesis of depressive and anxiety disorders. In particular, recent advances in the field of fear conditioning have provided valuable insight into the treatment of refractory depressive and anxiety disorders. In this review, we studied the reconsolidation-updating paradigm and the concept of epigenetic modification, which has been shown to permanently attenuate remote fear memory. This has implications for drug-augmented, e.g. antidepressant and valproic acid, psychotherapy. Future research on more sophisticated psychotherapy techniques will increase the desirability of this treatment modality for both clinicians and patients.

1. Introduction

Depressive and anxiety disorders are the most common psychiatric disorders. Major depressive disorder is a highly prevalent mental disorder affecting 15% of the general population during one's lifetime (Kessler et al., 2005). The lifetime prevalence of anxiety disorders is estimated to be around 30% in the US (Kessler et al., 2005).

In major depressive disorder, approximately 60% of patients benefit from antidepressant treatment. Remission rates achieved by initial antidepressant trials range from 35% to 45% (Thase et al., 2001). Three or more consecutive antidepressant trials have shown an increase in remission rate of up to ~65% (Quitkin et al., 2005; Rush et al., 2006). The remaining 35% of patients do not or only partially respond to antidepressant treatment. Considering relapses, the sustained remission rate decreases to 43% (Trivedi et al., 2006). Residual symptoms after treatment are not only debilitating, but also increase the risk of relapse or recurrence (Fava et al., 2007a).

Approximately 50% of patients with depression are treatment-resistant. Other than electroconvulsive therapy (ECT), few evidence-based treatment options are available for these patients. In the past few decades, the off-label use of psychotropic drugs and polypharmacy in the outpatient setting has increased (Mojtabai and Olfson, 2010). Despite the increasing prescription of antidepressants, the prevalence of depression has continued to increase (Compton et al., 2006). Furthermore, some researchers have suggested that long-term and excessive antidepressant therapy might modify the course of depression into a chronic and intractable disease (El-Mallakh et al., 2011; Fava et al., 2007b). In anxiety disorders, which share neurobiological aspects and treatment options with depression (Clark and Beck, 2010), patients with inadequate response to pharmacologic and non-pharmacological treatment represent up to 40% of the affected population (Bystritsky, 2006). Taken together, these findings indicate that current psychiatric treatment only meets the need of half of all patients. To fulfill the needs of the remaining half with treatment-resistant depression or anxiety disorder, we must continue to search for new therapeutic strategies with better efficacy.

The current set of techniques used for such treatment has increased to include repetitive transcranial magnetic stimulation (rTMS), vagal nerve stimulation (VNS), and deep brain stimulation (DBS). However, invasive procedures such as VNS and DBS should only be considered for the most treatment-refractory patients. In almost all cases, ECT is

Abbreviations: ECT, electroconvulsive therapy; DBS, deep brain stimulation; rTMS, repetitive transcranial magnetic stimulation; CBT, cognitive behavioral therapy; BDNF, brain-derived neurotrophic factor; EE, enriched environment; FC, fear conditioning; CS, conditioned stimulus; US, unconditioned stimulus; CR, conditioned response; HAT, histone acetyltransferase; HDAC, histone deacetylase; CREB, cAMP response element-binding protein; PTSD, posttraumatic stress disorder; mPFC, medial prefrontal cortex; DRN, dorsal raphe nucleus; VNS, vagal nerve stimulation; DG, dentate gyrus; HSV, Herpes simplex virus; FDA, Food and drug administration; fMRI, functional magnetic resonance imaging; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, N-methyl-D-aspartate; CIS, chronic immobilization stress.

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considered as the last resort for refractory mental illness. However, before turning to ECT, patients and clinicians should undergo sequential modification of the pharmacotherapy regimen with an interval of at least four to eight weeks. Ensuring the proper dosage and duration of drug treatment is important. If there is no response, the patient should be switched to other medications or to psychotherapy. If a partial response is noted, the medication should be titrated to the maximum tolerable dosage or combined with other medications with different mechanisms (e.g., atypical antipsychotics or mood stabilizers) (Lam et al., 2009; National Institute for Clinical Excellence, 2009). These trial-and-error-based approaches have remained essentially unchanged in the last decade.

However, new discoveries in the field of neuroscience have exciting implications for psychiatry. For example, optogenetics enables the temporospatial activation or inactivation of genetically-defined neurons with a high degree of accuracy (Adamantidis et al., 2014; Miller, 2006). This new technique will accelerate our understanding of the neural circuits of normal emotions and pathologic conditions such as depressive and anxiety disorders (Deisseroth, 2014; Deisseroth, 2012). This framework of dysfunctional neural circuits can help elucidate the development of new therapeutic strategies for treatment of psychiatric disorders.

Psychotherapy has evolved through empirical research during the last century and is used not only to modify behaviors, but also to modulate the neural circuit, as detectable with functional magnetic resonance imaging (fMRI) (Barsaglini et al., 2014). Though psychotherapy should be used as a primary or concurrent treatment option in treatment-resistant depressive and anxiety disorders, it is often overlooked and not used as an alternative or concurrent treatment modality. In the past two decades, the practice of psychotherapy remained less common than pharmacotherapy (Mojtabai and Olfson, 2008) in spite of the strong evidence that cognitive behavioral therapy (CBT) is just as or even more effective than first-line pharmacotherapy for anxiety and mood disorders. (Barth et al., 2013; Holmes et al., 2014).

Functional imaging studies underpinning therapeutic mechanisms of psychotherapy in depressive and anxiety disorders suggest that the top-down regulation of the subcortical areas by high-order cortical areas increases after a successful treatment (Linden, 2006; Messina et al., 2013; Otto et al., 2014). This macroscopic system-level approach provides valuable implications; for this, readers can refer to recent reviews (Linden, 2006; Messina et al., 2013; Otto et al., 2014). Here, we focus on molecular-, cellular-, and neural circuit-level approaches underpinning depression and anxiety disorders. Our work will provide valuable implications for psychotherapy and pharmacotherapy.

First, we will introduce clinical and preclinical evidence that the combination of pharmacotherapy and psychotherapy is superior to each therapy alone. Based on the neuroplasticity hypothesis, we suggest two prerequisite components to maximize the clinical effectiveness of treating depression and anxiety disorders. The first component is corrective experience based on reconsolidation-updating. To understand the theoretical background of the reconsolidation-updating discussed in Section 6, we summarize the learning theories and their implications for psychotherapy in Section 5. The second component is enhanced neural plasticity, for which we will show persuasive evidence that antidepressant and epigenetic priming by HDAC inhibitors synergistically enhance neural plasticity. Next, we scrutinize the potential of valproic acid, a class I HDAC inhibitor, to improve the clinical outcome of pharmacotherapy and/or psychotherapy in refractory depression and anxiety disorders. Finally, we propose the framework for future research of neurobiology-inspired plasticity-augmented psychotherapy.

2. Combination of pharmacotherapy and psychotherapy

After the era of psychoanalysis, psychiatrists are increasingly turning to pharmacotherapy for the treatment of depressive and anxiety disorders (Marcus and Olfson, 2010; Olfson et al., 2002). This tendency has influenced non-psychiatric physicians. Mark et al. reported that general practitioners wrote 62% of antidepressant prescriptions, and psychiatrists 21%, with the balance by other non-psychiatric physicians or non-physician prescribers in the USA (Mark et al., 2009). However, talk-based psychotherapies such as cognitive behavioral therapy and interpersonal therapy have been shown to be equally effective as antidepressant treatment (Elkin et al., 1989; Khan et al., 2012).

Pharmacotherapy has been the preferred treatment for both psychiatrists and patients because of its advantages in cost and time effectiveness. However, in the treatment of depression, it has been consistently reported that the combination of psychotherapy and pharmacotherapy is superior to pharmacotherapy alone (Schramm et al., 2007). Recent meta-analyses have suggested that the combination of CBT and antidepressant treatment is superior to antidepressants alone (Cuijpers et al., 2014; Hollon et al., 2014). This difference is remarkable considering that only a few antidepressants show slightly superior efficacy to others (Cipriani et al., 2009).

The CBT and antidepressant combination have also been reported to be superior to each therapy alone for the treatment of panic disorder (Barlow et al., 2000). In addition, CBT has shown superiority to antidepressant treatments in the maintenance therapy for anxiety disorders (Otto et al., 2004). One meta-analysis of the treatment of panic disorder revealed that combination therapy is superior to antidepressant treatment with regard to long-term outcomes (Furukawa et al., 2007).

3. Current hypotheses on the pathogenesis of depression and the mechanism of action of antidepressants

The first hypothesis on the pathogenesis of depression is the "monoamine hypothesis," from which almost all of the currently available antidepressants are developed. However, the 2–3 week gap between the peak of neurotransmitter increase and the therapeutic response suggests that depressive symptoms do not merely stem from neurotransmitter deficits. The discovery that antidepressants enhance neurogenesis in the hippocampus through the increase of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) has prompted the "neurogenesis hypothesis" (Eisch and Petrik, 2012; Sahay and Hen, 2007) and "neurotrophic hypothesis" (Duman and Monteggia, 2006; Lee and Kim, 2008). Recently, one unifying hypothesis integrating these theories has been called the "neuroplasticity hypothesis" and argues that the pathogenesis of depression is based on dysfunctional plasticity at the synaptic level (Duman and Aghajanian, 2012; Duman and Li, 2012). Adaptations to the environment are mediated by neural plasticity. Monoamine neurotransmitters such as serotonin (Huang and Kandel, 2007; Michael et al., 1998; Shomrat et al., 2010), dopamine (Li et al., 2003; Rossato et al., 2009; Sheynikhovich et al., 2013), and norepinephrine (Hu et al., 2007; Tully et al., 2007) can all modulate neural networks by affecting synaptic strength, a phenomenon known as synaptic plasticity. This hypothesis explains the rapid (within hours) treatment action of ketamine infusion and glutamate antagonists, which robustly increase synapse number and affect gene expression (Duman and Aghajanian, 2012). In addition, neuroinflammation (Kim et al., 2016) and neurodegeneration (Myint and Kim, 2014) hypotheses have also been proposed to account for the pathogenesis of depression.

4. Antidepressant effect is affected by environment

4.1. Clinical evidence of the interactions between antidepressants and the environment

It is generally accepted that the placebo effect accounts for 75% of the efficacy of antidepressants. Considering unpublished clinical trials, the contributions of the placebo effect increase to 82% (Kirsch, 2008; Kirsch et al., 2008). Because patient belief affects treatment, most randomized controlled clinical trials have assessed the efficacy of antidepressants compared to a placebo. In clinical trials, structured