

Rapid-Acting Antidepressants and Underlying Mechanisms

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ABSTRACT

Loss of glial cells with resulting atrophy of the medial prefrontal cortex (mPFC) as well as the hippocampal area is demonstrated in depressed patients by brain imaging and postmortem studies. The mPFC is the master control of mood and emotional response. The hippocampus is part of the limbic system, the main function of which is to regulate emotions. The mPFC depends on the hippocampus for rapid learning and memory consolidation. Unlike monoamine reuptake inhibitor antidepressants, which take 6 to 8 weeks to exert their full effects, and with 30-40% unresponsive rate, ketamine acts rapidly, within a couple of hours, and has higher responsive rates. It suggests that in theory, due to its rapid effect, Ketamine could well serve as a bridging remedy to lower the rate of suicidal risk before Selective serotonin re-uptake inhibitors (SSRIs) reach their full effect for long-term depression management. Yet, ketamine has long been linked with abusive potential and possible neurotoxicity if used in large doses over a prolonged period. Even though there are no collected data to prove the associated adverse effects, awareness of this negative aspect of ketamine is sufficiently widespread to propel the psychiatric community to look for other rapidly acting antidepressant alternatives. Recent studies have shown that scopolamine, the Yueju pill, and magnesium are rapid-onset antidepressants that have mechanisms comparable to that of ketamine. These rapid-acting antidepressant agents promise to be effective and safer choices for depression management in the future, providing for further studies and investigations to produce a better and fuller understanding of their effects and limitations.

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1. INTRODUCTION

Brain anatomical change and neurochemical shifts associated with depression have been observed in studies over the past 20 years [1-5]. The association between depression and neurobiology has led to further investigations focusing on the neuronal signaling pathways and neurotrophic factors, which can contribute to the morphological changes in the brain.

Because the symptoms of depression can be improved by agents that act to increase synaptic concentrations of monoamines, antidepressant management in the past five decades has been focused on the monoamine hypothesis, which proposes that the underlying neurobiological basis for depression is a deficiency of noradrenergic and serotonergic systems, so that targeting of this neuronal lesion with a monoamine antidepressant could restore normal brain function [4]. In spite of that, less than one-third of major depression disorder (MDD) patients receiving standard antidepressants experienced remission after up to four months of treatment [6]. Typical SSRIs take six to eight weeks to alleviate depression symptoms. During this lag period, there is the risk of lapses in treatment, and of increasing suicidal ideation.

Undoubtedly, it is urgent and providers are obliged to develop faster acting and more effective antidepressants.

Ketamine, an anesthetic medication, was first reported to have therapeutic effects in MDD in year 2000 [7]. Ketamine, a rapid antidepressant, is N-Methyl-D-aspartate (NMDA)-receptor non competitive antagonist, and it upregulates brain-derived neurotrophic factor (BDNF) expression. BDNF is a member of the neurotrophin family of growth factors. Ketamine targets glutamate, the main excitatory amino acid neurotransmitter in the brain. Over-activation of the NMDA receptor by glutamate can lead to excitotoxicity, synaptic degradation, and neuron apoptosis. NMDA-receptor antagonists reduce glutamate binding and therefore decrease the excitotoxicity of neurons. One randomized controlled trial (RCT) of ketamine was conducted in treatment-resistant depression patients, including patients who had not responded to antidepressants with satisfactory therapeutic results [8]. Treatment-resistant depression refers to cases of MDD that do not respond satisfactorily to appropriate courses of at least two antidepressants [9]. Preclinical studies have indicated that repeated daily ketamine administration may have neurotoxic effects, particularly on the function of GABAergic interneurons [8]. The abusive potential and neurotoxicity possibility of ketamine warrant the search for alternative rapid-acting antidepressants. Scopolamine was found to reduce symptoms of depression within three days of the first administration [10-12]. The Yueju pill, an ancient Chinese herbal formula designed to treat mood disorders, is still popular today and found to be a rapid-onset antidepressant working through NMDA receptors and BDNF expression [13-15]. The level of magnesium, another NMDA-receptor antagonist, is found to be lower than normal in Treatment-resistant individuals [16-17].

These findings raise a number of questions. First, how might depression cause the atrophy of neurons, and under which signaling pathways, and neurotrophic factors? Second, how might ketamine reverse neuron damage and brain morphological changes? Third, how might scopolamine, the Yueju pill, and magnesium, produce a rapid antidepressant effect similar to that of ketamine?

To clarify these concerns, we reviewed a large body of available clinical studies with patient data on ketamine antidepressant effects, studies of magnesium and scopolamine along with preclinical animal experiments of the Yueju pill. We discuss research that associates atrophy of the limbic system and the cortex with depression. We examine the effect of depression in terms of neurobiology and the promising novel rapid antidepressants. This article outlines the study background, important results, and the linkage of the underlying mechanisms of rapid-acting antidepressants.

2. RESEARCH METHOD

We used universal standards for qualitative research study when selecting articles and ensuring quality of the studies reviewed. The followings are criteria to include articles in the sample: (a) published in a peer-reviewed journal from 2000 to 2014; (b) cited in medical or related literature; (c) main focus on topic of rapid-acting antidepressants. Prospected articles were obtained by accessing PubMed database. Key words used included Treatment-resistant depression, ketamine, NMDA-receptor, glutamate, Yueju pill, and magnesium. Database searches combined yielded 50 articles for possible inclusion in the sample. Abstracts of articles were read to determine whether to obtain full texts of the studies. If the abstract of an article revealed the exclusive use of standardized data collection tools, and other quantitative measures, the article was not reviewed further. Articles that focused on rapid-acting antidepressants with qualitative methods were evaluated to be included in the sample. Based on the criteria for inclusion, the researchers selected 32 articles for the final sample. The focus of this paper was to analyze collective findings of qualitative studies on the broad topic of rapid-acting antidepressants. Each research study was carefully reviewed and summarized by the researchers according to this agenda, which included the following criteria: sample, research design, data analysis, and primary findings.

3. RESULTS AND ANALYSIS

3.1. Epidemiology of Depression

Major depression disorder (MDD) is one of the most common prevalent lifetime mental disorders in the United States, affecting approximately 16.6% of the general population. According to the World Health Organization (WHO; 2010), major depression also carries the heaviest burden of disability among mental and behavioral disorders. Major depression is a mood disorder characterized by a sense of inadequacy, despondency, decreased activity, pessimism, anhedonia and sadness, where these symptoms severely disrupt and adversely affect the person's life. Further, depression is a life-threatening condition, preventing some patients from performing activities of daily living or causing self-destructive behavior, even suicide attempts.

3.2. Neurobiology of Depression

Brain imaging studies of depressive patients reveal volume reduction in limbic brain regions: notably in the hippocampus and mPFC [1-2]. Post-mortem studies report a reduction of neurons and loss of glia. These studies confirm a well-established connection between loss of neurons and depression-related disorders. Neurotrophic factors play a major role in cell atrophy, and are supported by evidence that depression decreases certain neurotrophic factors in limbic brain regions. BDNF is one of the most studied neurotrophic factors. A reduction of BDNF in depressed subjects was revealed in post-mortem studies. This work suggested that BDNF is a significant biomarker of depression and treatment response [18-19]. On the other hand, antidepressant treatment elevates the expression of BDNF in the hippocampus and PFC [20]. Evidence also shows that antidepressant treatment is correlated with increases in BDNF in post-mortem brains of subjects on antidepressants at the time of death. Besides BDNF, there is evidence that links other neurotrophic/growth factors with depression, such as vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF-2), and insulin-like growth factor 1 (IGF-1). We further find depression and antidepressant treatments have contrasting effects on the expression of these factors. The "Neurotrophic hypothesis of depression and antidepressant response" proposes that depression results from decreased neurotrophic support, which causes neuronal atrophy, decreased hippocampal neurogenesis and loss of glia; antidepressant treatment reverses this deficit, and thereby reverses the brain atrophy and neuron loss [21]. Neuroplasticity is found to play a major role in mood disorders. During depression progression, neurogenesis, neuron dendrites, and synaptogenesis are altered by stress and antidepressant treatments. Increasing activities of neurons cause the insertion of glutamate receptors and the formation of spine synapses [22].

3.3. Standard Antidepressants

The typical antidepressants include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin modulators (SMs), tricyclics (TCAs), and monoamine oxidase inhibitors (MAOIs). SSRIs are the newer agent and the most widely prescribed and standard antidepressants in the treatment of MDD. The reason for such antidepressants being the first-trial antidepressant treatment choice has mainly come from the monoamine hypothesis, which is based on practical experience, and improved tolerability compared with older antidepressants. However, close to one third of MDD patients failed to remit after undergoing standard SSRIs antidepressant treatment [6].

3.4. Ketamine

Before conventional antidepressant treatment becomes effective, usually over a period of one to two months, patients can discontinue the medication, resulting in increased suicidal risk [23-25]. As a result, the discovery of treatments with a more rapid onset action became a major goal of biological psychiatry. The first drug found to produce rapid improvement in mood was the NMDA glutamate receptor antagonist, ketamine that demonstrates rapid and effective symptom relief in treatment-resistant patients with major depression. Recent clinical and animal studies reveal that a subanesthetic dose of ketamine can rapidly alleviate depressive symptoms, and its effect can last a few days to a week long [26]. Experimental studies also suggest that the rapid enhancement of BDNF expression and synaptic plasticity in given brain regions are responsible for this effect [27].

One study suggests that ketamine-induced antidepressant effects are associated with α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors-mediated upregulation of the mammalian target of rapamycin complex 1 (mTORC1) and BDNF in the rat hippocampus and prefrontal cortex [20]. The NMDA-receptor is pre-synaptic, while the AMPA-receptor is post-synaptic. mTORC1 is a key transcription agent that amplifies the frequency of excitatory postsynaptic currents, and extracellular glutamate in the mPFC. Another report suggests that ketamine deactivates the eukaryotic elongation factor 2 (eEF2) kinase, leading to reduced eEF2 phosphorylation and therefore an increasing translation of BDNF. Furthermore, a single dose of ketamine induced a rapid and complete reversal of spine deficit and function caused by three weeks of chronic, unpredictable stress exposure [21]. Based on case studies, open-label surveys, and controlled trials up to date, Ketamine can be a novel option with less adverse effects for treatment-resistant depression patients who have tried and failed two or more antidepressant medications, and electroconvulsive therapy (ECT) [9]. There are also reports that ketamine is effective for treatment of suicidal emergency [23-25]. However, lack of long-term follow up data and its potential for abusive use have restricted the provision of ketamine infusions to clinics and hospital settings, where they can be administered under the supervision of medical professionals.

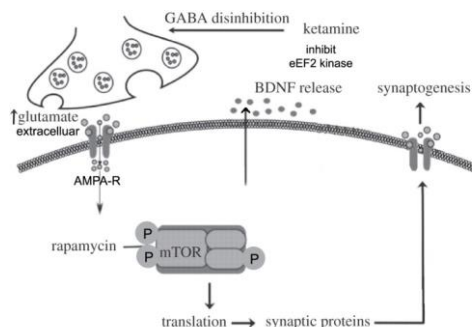


Figure 1. Edited Picture from Duman et al 2012 [28]

3.5. Scopolamine

Clinical studies report that scopolamine, a muscarinic receptor antagonist used for motion sickness, produces rapid antidepressant effects in depressed patients [10]. Similar to ketamine, scopolamine increased signaling by mTORC1, which is connected to the rapid actions of NMDA-receptor antagonists [11-12]. The results confirm that the antidepressant actions of scopolamine involve mTORC1 signaling, increased glutamate transmission, and synaptogenesis, thus acting in a manner similar to NMDA-receptor antagonists. One randomized, double-blind, placebo-controlled RCT investigation examined the efficacy and safety of scopolamine in moderate-to-severe MDD, and the augmentation with scopolamine was significantly more effective than the placebo [10]. Patients receiving scopolamine showed higher rates of response (65%) and remission (65%) than the placebo group (30%). Scopolamine blocks the muscarinic receptor, which is thought to be overactive in patients with MDD.

The efficacy of scopolamine through the blockade of muscarinic receptors is also the same mechanism as that of tricyclic antidepressant medications (TCAs), the oldest type of antidepressants. With TCAs, the muscarinic receptor blockade was viewed as the cause of undesired cholinergic side effects. For that reason, the newer antidepressants, such as SSRIs or SNRIs, were specially designed to avoid the muscarinic-receptor antagonist effect. It is, however, a common consequence for patients treated with scopolamine to present with higher rates of dry mouth, blurred vision, and dizziness.

3.6. The Yueju Pill

“Yueju” means “escaping depression” in Chinese. It was formulated 800 years ago by a famous Chinese doctor, Danxi Zhu. It is still popularly prescribed today to treat depression and loss of appetite. Yueju is composed of five equal amount of herbs, Xiang Fu, Chuan Xiong, Zhi zi, Cang Zu, and Shen Qu. Animal preclinical studies have shown that Yueju is an effective antidepressant [13-15]. It has been previously reported that ethanol extract of Yueju has antidepressant effect after a week-long administration [15]. In addition, only a single Yueju ethanol extract administration is needed to demonstrate a rapid antidepressant effect in the Learned Helpless Paradigm. It significantly reduced the number of escape failures. The latency to escape also showed a trend to decrease in Yueju-treated mice [13]. Many active components in Yueju are essential oils that may be extracted with ethanol, such as α -cyperone and β -cyperone in Xiang Fu and atractylin and hinesol in Cang Zhu [15], [29]. The effective components of Yueju regulate glutamate in a way similar to ketamine, and require further investigation.

Yueju, similar to ketamine, rapidly increased the expression of BDNF in the hippocampus, whereas the BDNF mRNA expression remained unaltered [13]. This is likely to have resulted from posttranscriptional regulation. Yueju rapidly reduced the phosphorylation of eEF2 in the hippocampus, leading to the desuppression of BDNF synthesis. BDNF protein expression was rapidly increased by Yueju, and antidepressant-like effects of Yueju were sustained for 24 hours in mice, but decreased after 24 hours. In contrast, eEF2 was continuously dephosphorylated in ketamine-treated mice at 24 hours [13]. Yueju, as an herbal medicine, is found to be effective and lasting as a rapid antidepressant comparable to ketamine. The fast induction of BDNF may be the underlying mechanism responsible for the rapid antidepressant action of ketamine and Yueju. This discovery opens a new path to seek better alternative management for MDD. However, the dosage amount used in (Xue W, et al, 2013) is much higher than the recommended prescription used in depressed patients.

3.7. Magnesium

Magnesium Deficiency can subject patients to neuropathology. Magnesium ions regulate calcium ion flow in calcium channels. Calcium and glutamate are both excitatory, and in excess, neurotoxic. Calcium activates the NMDA receptor. Magnesium deactivates NMDA receptors, of which the main functions are synaptic plasticity control and memory formation. In magnesium deficiency, neuronal damage from overly activated neuronal receptors could manifest as depression [16], [30]. These magnesium ion neuronal deficits may be induced by stress hormones, dietary deficiencies of magnesium as well as excessive dietary calcium. Refined flour contains only 16% of the magnesium found in whole wheat. Excessive alcohol drinking can also deplete magnesium storage in the body. Case studies showed rapid recovery, less than 7 days, from MDD using 125-300 mg of magnesium four times a day [17]. The possibility that magnesium deficiency is the cause of most MDD is of enormous importance to public health, in that it affects the population at large, and is therefore recommended for further and advanced research. Nonetheless, magnesium deficiency can be ameliorated easily by the consumption of whole grains and/or nutritional supplements. This simple implementation can prevent or at least lower the incidence of MDD and the undesirable outcomes associated with it.

4. DISCUSSION

Current conventional antidepressants act slowly, and it is urgent to develop the therapeutics that can quickly and enduringly treat depression. In an effort to elucidate the mechanisms of rapid-acting antidepressants implicated in treating major depression disorder, we conducted a thorough literature review on the most recent research related to fast-onset antidepressants and their related mechanisms.

The reason that depression causes cortical atrophy can be answered best with the theory known as “Neurotrophic hypothesis of depression”, which states that depression results from decreased neurotrophic support, which causes neuronal atrophy, decreased hippocampal neurogenesis and loss of glia. Reduction of BDNF is also found in depressed subjects.

Ketamine reverse neuron damage by deactivating eEF2 kinase, and increasing the translation of BDNF, which regulates neuronal survival and differentiation. Consequently, ketamine stops the morphological changes of the brain due to depression.

The possible reason that ketamine acts fast globally is that it works against glutamate, the main excitatory neurotransmitter present in more than 50% of nervous tissue. Traditional antidepressants act through monoamines, such as serotonin and dopamine, which are only present in 15% of nervous tissue. It is exciting to discover the mechanism of novel rapid-acting antidepressants such as ketamine, scopolamine, the Yueju pill, and magnesium and their relationship with glutamate.

It is understood that the deficits in different forms of neuroplasticity, including synaptic mechanism and neurotrophic mechanism, are responsible for depression [19], [31]. BDNF is the best studied neurotrophic factor concerned in depression. Increasing numbers of studies support the view that BDNF is necessary for mediating antidepressant effects [18]. Typical monoamine antidepressants increase BDNF only after long-term administration [5]. After being carefully studied and examined, the mechanisms of the recently discovered rapid-acting antidepressants, the linkage and interactions between glutamate, mTORC1 signaling, BDNF, and synaptogenesis are the key to understanding depression. Further research focused on these areas will help to develop safer and more effective rapid-acting antidepressant agents.

To our knowledge, this is the first and only study that reports the connection between different rapid-acting antidepressants and the mechanisms behind their actions. Decreasing glutamate transmission allows neurons to rest and gives them the opportunity to regenerate. Enhancing BDNF expression indicates upregulation of neuroplasticity, which is found in many studies to alleviate depression symptoms. Sufficient evidence supports the function of BDNF in the survival and differentiation of neurons. BDNF employs acute effects on the transmission and plasticity of synapses, and heightens excitatory synaptic transmission. Our recent studies have revealed a novel cooperative interaction between BDNF and glutamate in the regulation of dendritic development. These studies draw attention to the significance of the collaboration between BDNF and glutamate in the regulation of synaptic transmission and neuronal development.

5. CONCLUSION

The present studies advocate the association of depression with glutamate and BDNF in ketamine, scopolamine, the Yueju pill, and magnesium for future antidepressant development. Clarifying the relationship of glutamate, BDNF and the signaling pathways might help to understand the exact contribution of neuroplasticity and permit diagnostic and therapeutic advances in depression management. Although these findings pave the way to a theoretically different approach to the treatment of depression, it awaits additional

studies for rapid-acting antidepressants to become clinically practicable. This possibility needs to be established empirically in studies to demonstrate rapid-acting antidepressant treatments can be implemented with less adverse effects, transitioned to long-term treatment, and management for major depression disorder.

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