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Neurobiological Augmentation of Psychotherapy in Treatment Resistant Depression

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Abstract

A substantial number of patients diagnosed with major depression disorder have poor or no response to standard antidepressive drugs. Recent studies showed that ketamine promotes a rapid and sustained antidepressive effect and also promotes neuroplasticity in the regions involved in MDD psychopathology.

In this review we summarize the molecular mechanisms of ketamine action, behavioral changes upon administration and the psychotherapeutic implication of ketamine-induced modification of learning and memory processes. Then, from a multi-point perspective, we argue for possible long-term benefits of NMDA receptor modulation on psychotherapy in patients with major depressive disorder. We embed this proposed augmentation strategy into existing literature on the role of NMDA-receptor mediating learning and conclude on recent psychotherapeutic implications for the use of ketamine within multidimensional treatment consideration.

Keywords: Ketamine; Learning; Memory; Psychotherapy; Neuroplasticity; Depression

Introduction

Neuroplasticity is the capacity of the brain to reorganize its structure and functions in response to intrinsic or extrinsic stimuli [1]. Therapeutically, these changes may occur as a consequence of pharmacological interventions dubbed by psychotherapy [2] or very elaborate noninvasive interventions such as neurofeedback training [3,4]. Thus, neuroplasticity-based therapy conceptually moves beyond the simple focus of symptom alleviation and management.

The recognized deficit in neuroplastic capacity of several psychiatric disorders, among them Major Depressive Disorder (MDD) can be alleviated by pharmacological intervention (see e.g., [5]). The Brain-Derived Neurotrophic Factor (BDNF) is a member of the neurotrophin family of growth factors, and is critically involved in regulating the survival and differentiation of neuronal population during development [6]. In MDD, inadequate BDNF secretion in brain region such as hippocampus was for example associated with the dysfunctional neural circuitries of emotion-perception [7]. With a symptomatology that is dependent on the route of administration [8], BDNF levels in MDD patients were shown to have a strong association with depression scores. Hence, the association between MDD symptom alleviation and neuroplasticity can be sufficiently supported by recent work (reviewed in [9,10]).

Conventional antidepressants target mainly monoamine levels to alleviate symptoms. However, the timeframe in which these drugs reach the efficiency peak spans over a few weeks within the treatment period. This delay enhances the risks associated with severe patients [11] including suicide for the worst.

Ketamine, an antagonist of N-methyl-D-aspartate (NMDA) receptor, is a rapid antidepressant that targets the glutamate systems. Recent clinical trials have shown that a single trail of low dose ketamine produces rapid antidepressant response, reaches the highest effect at 24 hours and lasts up to 7 days [12]. The mild psychotomimetic and dissociative effects - caused by the acute blocking of the excitatory glutamate NMDA receptor - completely dissipate within 80 minutes after ketamine administration [12,13]. The rapid antidepressant effect of ketamine is especially common in treatment-resist depression patients (TRD) [14].

Many of the major depressive disorder (MDD) symptoms can be associated with a biased cognitive function. Functional neuroimaging and lesion studies have emphasized the large overlap between the regions involved in reversal and reinforcement learning, and those showing abnormalities in MDD psychopathology. For example, both reinforcement and reversal learning share dopaminergic pathways that send impulses to the nucleus accumbens and to prefrontal cortex (PFC) [15]. In turn PFC structural and functional abnormalities contribute to cognitive deficits associated with MDD [16].

In this study we summarize the molecular neurobiology of ketamine, the behavioral changes upon administration and the psychotherapeutic implication of ketamine in learning and memory process.

Neurobiological mechanism of ketamine as an antidepressant

Ketamine produces a rapid antidepressant response that reaches the highest effect after 24 hours and lasts up to 7 days [12]. Acute blocking excitatory glutamate receptor, ketamine infusion causes mild psychotomimetic and dissociative effects 30 minutes after ketamine infusion and this effect dissipating 80 minutes after administration [12,13].

In low doses, ketamine blocks NMDA receptors and increases the extracellular glutamate level which, in turn, stimulates postsynaptic non-NMDA receptors - such as AMPA/kinase receptor (α-amino-3-hydroxy-5-methylisoxazole-4-propionate) [17]. AMPA receptors play an essential role in ketamine related antidepressant effects: a) subcutaneous treatment with 2,3-dihydroxy-6-nitro-7-sulfoamoylbenzo(f) quinoxaline (NBQX), an AMPA receptor antagonist, induces a blockage of ketamine antidepressant effect in both acute (30 minutes) and sustained (72 h) phase [18]; b) chronic treatment with low dose ketamine results in increased AMPA/NMDA receptor density ratio in the hippocampus [19]; c) low dose of ketamine activates mammalian target of rapamycin (mTOR) pathway in postsynapse increasing synaptic signaling proteins such as 4E-BP1 (eukaryotic initiation factor 4E binding protein) and p70S6K (p70S6 Kinase) within two hours after injection [20]. Activation of mTOR pathway triggers synaptic protein synthesis: a single dose of ketamine significantly increases levels of activity regulating cytoskeletal protein (Arc) within one hour, as well as glutamate AMPA receptor-1 (GluR1), postsynaptic density protein-95 (PSD95) and synapsin I after two hours. The prolonged induction of GluR1, PSD95 and synapsin I remained elevated up to 72 hours after ketamine treatment resulting in increase synaptogenesis [20]. This effect increases number of mature dendrite spines - as well as the serotonin (5-HT)- and hypocretin-induced excitatory post-synaptic currents (EPSC) in PFC - indicating a facilitation of synaptic plasticity.

Acute stress and depression induces neuronal atrophy in prefrontal cortex (PFC) and hippocampus [21,22], mediated by NMDA receptors activation [23]. A decrease of dendritic spines in hippocampus is frequently found in depression animal models [24]. Human studies reported decreased PFC and hippocampus volume in depressed patients [16]. The neuroplastic effect of ketamine might counteract these effects therefore improving the cognitive control deficit related to depression.

Molecular evidence of ketamine in prolonged (24 hours) learning facilitation

The activation of NMDA receptor results in postsynaptic depolarization through AMPA receptors. The binding glutamate allows Ca2+ to enter the postsynaptic neuron inducing synaptic plasticity changes - especially long-term potentiation (LTP) - and activating downstream neural pathways, e.g., cyclic adenosine monophosphate (cAMP), protein kinases, cAMP-response-element-binding protein (CREB) and regulating gene expression [25,26].

NMDA receptors are regarded as one of the key proteins in hippocampus-dependent memory. They overexpress the NR2B receptor subunit of the NMDA receptor enhancing learning and memory performance in animals [27]. Most pharmacological studies using NMDA receptor antagonists found impaired learning and memory in acute phase, suggesting disrupted memory pathways shortly after NMDA blockage [28]. Nevertheless, treatment with dizocilpine (MK801) - NMDA receptor nonselective antagonists - has been shown to improvement short-term memory acquisition in step-down passive avoidance task, i.e., avoidance of a noxious event by suppression a particular behavior [29]. Low dose of dizocilpine (0.01 mg/kg) facilitates long-term habituation activity in a spatial novelty test in Napel low excitability rats line with lower behavioral arousal to novelty [30]. However, this enhanced learning effect by NMDA receptor antagonists can be argued by non-associative factors such as anxiolytic activity or motor activation of these types of learning paradigms [31].

So far, to the best of our knowledge, few studies focused on the effects of NMDA receptor antagonist after its half-life (circa 180 minutes in humans [32]). Recent studies on the neural signal pathways of ketamine have started to provide evidence of sustained, beneficial role of ketamine.

The first evidence derives from the AMPA-dependent learning, especially in the context of emotion. Emotional arousal-induced endogenous stress hormone release, e.g., noradrenaline, negatively impacts memory formation by phosphorylation of AMPA receptor GluR1 subnunit, lowering the threshold for trafficking to the synapse [33]. Stress studies indicate that acute stress can weaken memory via the removal of synaptic AMPARs [34,35]. Thus, stress hormone mediates irregularities in AMPA receptor plasticity underlining neurological dysfunctions following traumatic events causing psychiatric disorders, e.g., major depression and general anxiety disorders [36]. Studies using both GluR1 knockout mice and normal mice found that AMPAR trafficking (especially GluR1) is required in amygdala-dependent learning [37,38]. As described above, AMPA receptor augmentation still exists when NMDA receptor blockage by ketamine stopped; it is very likely that a learning facilitation effect will start at this time point.

Secondly, both rapamycin treatment and genetic studies revealed the importance of mTOR signaling in memory (reviewed in [39]). New protein synthesis is crucial for long-term memory and is accompanied by an increase in the number of mature synapses [40,41]. In 6-24 hours delayed time point after ketamine treatment, the activated mTOR signal-pathway induced protein synthesis and psynaptogenesis. New protein synthesis and psynaptogenesis provide possibility for establishing new memory trace therefore very likely enhances learning and memory [42].

Thirdly, AMPA receptor regulation of synaptic function involves the activation of voltage-dependent calcium channels (VDCCs) and activity-dependent release of brain-derived neurotrophic factor (BDNF) [43,44]. Positive AMPA receptor modulators induce increased BDNF, mRNA (messenger RNA), protein kinase B protein-activate (PKB/Akt) and extracellular signal-regulated kinase (ERK). This prompts the activation of mTOR in dendrites and the synaptoneurosome fraction which upregulates the local protein synthesis [45], facilitates LTP and increases synaptic transmission [46]. This mechanism facilitates memory formation [47].

In the past decades, large number of studies suggested that BDNF plays a crucial role in learning and memory [48,49]. Molecular studies found that BDNF facilitates glutamate release and increases

phosphorylation of the NMDA receptor NR1 and NR2B subunits and up-regulates GluR1 AMPA-receptor expression and phosphorylation thereby highly involved in LTP [50]. The changes in BDNF levels are directly associated with depression- and anxiety-like behavior [51]. Post-mortem studies have shown an association between depression and: i) a decrease of BDNF (and CREB) concentration in the hippocampus [52]; ii) an increase of BDNF (and CREB) concentration in the nucleus accumbens (NAc) [53,54]. The single nucleotide polymorphism (SNP) Val66Met of the BDNF gene influences the activity-dependent secretion and intracellular trafficking of BDNF [55]. Knock-in mice, that homozygously express Met66 BDNF, showed more anxiety-like behavior and a greater resilience to behavioral and molecular changes after social defeat [53,56]. Both knock-in mice and human Met carriers show impaired conditional fear extinguish response. This suggests that BDNF plays a role in anxiety disorders with impaired learning of cues that signal safety versus threat [57]. Further, human polymorphism studies indicated that the Met alleles are associated with abnormal hippocampal neuronal function as well as impaired episodic memory [58]. However, later human studies have suggested that BDNF trafficking change does not influence all memory types. In particular, no association of the BDNF genotypes with declarative memory and working memory was observed [59,60].

In addition, a recent study found that ketamine persistently enhances induction of LTP of synaptic transmission 24 hours after injection and increases the NMDAR-NR2B concentration on cell surface at rat hippocampus and medial PFC (MPFC) synapses in vitro [61]. Regarding the importance of NR2B subunit in hippocampus-dependent memory, it underpins the memory beneficial effect of a single dose ketamine at 24 hours.

Behavior evidence of ketamine in learning facilitation effect and perspective

Encoding and retrieval

Ketamine is known to produce robust episodic memory impairments, to disrupt semantic memory and to impair error monitoring during execution [62]. It might also be related to declarative memory task deficit through its effect on manipulation rather than maintenance of information in working memory [62]. The deleterious effects of ketamine on episodic memory rely more on encoding process rather than retrieval, as a number of studies have shown [63-67]. Honey et al. [68] found that low dose ketamine administered at retrieval reduces guessing tendencies for answers - opposite to the effect if administered at encoding – and suggested that ketamine improves memory recall performance by facilitating encoded memory. Another study found that when administered immediately after the introductory session or before the recognition session, NMDA receptor antagonist MK-801 induces increased interest for the novel object reflecting retention facilitation [69]. Taken together, these studies have shown that ketamine impairs encoding and facilitates retrieval.

Sustainability

However extensive this evidence is, the sustainability effect of ketamine remains poorly understood. A recent study reported post ketamine infusion enhancement of reconsolidated memory occurring after 24 hours. This effect was associated with the psychotic symptoms resulted from excessive glutamate release [70]. Enhanced memory consolidation and reconsolidation was also found 24 hours after memantine - an NMDA receptor antagonist - administration in day-old chicks [71]. Thus, it seems that NMDA receptors antagonist is relevant for memory process.

However, chronic ketamine users shown increased D1 receptor (dopaminergic receptor) concentration in right dorsolateral prefrontal cortex, suggesting that elevated D1 receptor up-regulation might be a compensatory mechanism for drug-induced deficit [72].

Learning, reward and cognitive flexibility

In reinforcement learning the agent learns as a consequence of its actions. This process, eminently of a trial-and-error nature, can be doubled by the presence of rewards or by punishments avoidance (reviewed in [73]). A recent study found that NMDA receptor uncompetitive (but not competitive) antagonists such as ketamine, significantly increase impulsive choice. This observation is preferential to low-impulsive rats [74]. Functional neuroimaging and lesion studies showed that some brain regions are common to both reinforcement and reversal learning, such as the nucleus accumbens and the PFC (especially the ventromedial PFC (vmPFC)) [75,76] that involved in dopaminergic pathways [15], as well as orbitofrontal cortex (OFC) [77], dorsolateral PFC (dlPFC) [78] and dorsal anterior cingulate cortex (ACC) [79].

For a later discussion, it is noteworthy to emphasize the large overlap between the regions involved in reversal and reinforcement learning, and those showing abnormalities in MDD psychopathology. This overlap might explain the cognitive deficit present in MDD.

In humans acute administration of ketamine impairs attentional set-shifting indicating cognitive inflexibility [80-82]. However, little is known about the timeline of this inflexibility. Some evidence may be considered from animal studies where in an attentional set-shift task, in mice, a high dose (10 or 20 mg/kg) of ketamine, administered 50 minutes prior to sessions, worsened the performance by increasing the necessary number of trials, the time and the errors to reach the criterion. In the same experiment, ketamine administration (10 mg/kg) 3 or 24 h prior to sessions showed normal performance [83]. These findings provide some evidence that for the attentional set-shifting tasks, ketamine has different effects in acute and sustained phase.

As seen above, some studies investigating reinforcement learning, set-shift task, and reversal learning reported ketamine impairment after acutely administration, while others reported a facilitation effect. However, acute ketamine caused cognitive inflexibility but this effect disappears even before drug's half-life [12]. This might not be the case with the effect of ketamine on cognitive flexibility changes.

Major depression, neuroplasticity, ketamine and psychotherapy

MDD is characterized by a cognitive bias towards negative stimuli [84]. In vulnerable people special environmental circumstances can trigger an activation of depressive self-referential schemas like “I am worthless”. This schema activation can lead to biased attention, biased processing and biased memory of emotional internal and external stimuli which causes depressive symptoms and reinforces the self-referential schema. Neurobiological correlates of biased attention were found in the PFC, ACC and superior parietal cortex (SPC). In MDD, decreased functional activity in ventrolateral PFC (associated with

control over stimulus selection), in dorsolateral PFC (associated with executive functioning), in rostral ACC (important for inhibitory processing) and in SPC (involved in coordination of shifts in gaze) leads to a focus on negative stimuli. A hyperactivity of thalamus, amygdala and subgenual ACC together with a lack of inhibition via dorsal ACC is exemplary for the biased processing of negative stimuli and leads to an increased processing of negative stimuli. Biased memory and rumination are caused by altered functional activity mentioned above together with hyperactivity in hippocampus induced by negative stimuli (reviewed in [85]).

MDD patients show a higher sensibility towards learning by punishment, and a lower sensitivity towards learning by reward [86-88]. These findings crucially link to the clinical symptom of anhedonia, a main constituent of MDD core symptoms [89]. However, the bias towards learning by punishment in patients suffering from MDD leads to an overall worse performance in reward related learning [90]. The change in sensitivity was also found in reversal learning paradigms and related to the brain area striatum [91]. Furthermore, MDD patients shown impairment cognitive flexibility and memory [92,93], functions proposed to play a crucial role in reversal learning. These findings concur with studies showing that MDD is associated with prefrontal cortex (PFC) and the hippocampus structural and functional dysfunction [16].

Apart from task functional magnetic resonance imaging (fMRI) studies, resting state fMRI (rs-fMRI) studies found decreased functional connectivity of the default mode network (DMN) 24 hours ketamine post infusion [94]. The DMN network (a) consists of the pregenual anterior cingular cortex (pgACC), the medial PFC and the dorsal nexus (DN) located in the dlPFC, (b) shows a higher activity in resting state than in goal directed tasks, and (c) is believed to be a network of relative inactivity [95]. MDD patients showed DMN hyperactivity [96] and decreased ability to interrupt the activity of the DMN [97,98], which has been linked the inability to quit rumination and concentrate on a task [99]. The decrease in functional connectivity of DMN induced by ketamine might lead to a higher ability to work on goal directed tasks and thus reversal learning which heavily relies on executive functions and cognitive flexibility. However, this hypothesis needs further investigation.

Acute ketamine administration has a negative impact on reinforcement learning and reversal learning. There are no studies about a delayed effect on learning, but the mechanisms that were found to explain the antidepressive impact of ketamine hint to a possible improvement in learning, in general, and especially to reinforcement learning and reversal learning. This might, besides relieving certain MDD symptoms, lead to a benefit in psychotherapeutic sessions for MDD patients. Reversal learning as the ability to unlearn associations and learn new ones might be helpful to unlearn maladaptive thought patterns - as frequently seen in rumination - and to learn new ones. We can also hypothesize a change in the bias towards learning by punishment in MDD since, in monkeys, ketamine was found to modify the dopamine turnover in the striatum [100].

Cognitive behavioral therapy is often used as integral addition to pharmacotherapy for primary care based patients with treatment resistant depression [101]. Cognitive behavioral therapy (CBT) teaching patients to recognize, to proof and to modify their biased perception and biased processing aids patients, as soon as they learn how to connect their biased perception to new experiences, in that negative feelings will be less intense and patients will be able to cope better with the demands of daily life [102]. Another behavior therapy that specifically designed for patients with chronic depressive disorders is CBASP (cognitive behavioral analysis system of psychotherapy). In the therapeutic setting with a focus on interpersonal interactions, the patient learns to change maladaptive patterns of interpersonal behavior through new experience related learning [103]. Importantly CBASP directly focuses on generating novel experiences and their conceptual integration via negative reinforcement, a mechanism which may offer distinct molecular targets addressable by pharmacological augmentation. Nevertheless most behavioral therapies are largely based on patients' ability to learn new thoughts that could inhibit or replace the old biased, automatic thoughts as we described above. The neurobiological augmentation by single dose ketamine treatment, as described before, might have increased effictiveness when combined with other psychotherapies. Cognitive therapy focuses on the top-down control of the limbic brain areas and shows to modulate prefrontal-limbic functioning in depressed patients [104]. These structures were also showed to enhance neuroplasticity induced by ketamine treatment [105]. In addition, it was evidenced that the psychoactive effect of ketamine treatment facilitates psychotherapeutic intervention [106,107].

Neuroplasticity is the capacity of the brain to reorganize its structure and functions in response to intrinsic or extrinsic stimuli [1]. These changes occur as a consequence of pharmacological interventions dubbed by cognitive behavioral psychotherapy [2], neurofeedback training [3,4], mental rehearsal and learning of cognitive tasks [108,109], and non-verbal emotion communication training [110]. The characterization of such changes ranges from a molecular perspective to a behavioral one [5]. It is then reasonable to conclude, "plasticity is an obligatory consequence of all neural activity - even mental practice" [111]. At a molecular level the glutamatergic system is relevant to neuroplasticity as well as long-term cell growth/atrophy [112]. As a consequence, abnormalities within neural plasticity contribute to the pathological processes underlying mood disorders [113]. Ketamine showed beneficial effects in treatment resistant depression (TRD) patients [14], through enhancing AMPA receptor function, altering glutamatergic neurotransmission in prefrontal limbic circuitries and leads to neuroplastic adaptations [105].

Conclusion

We reviewed here emerging evidences that speak in favor for an augmentation of psychotherapeutic learning via glutamatergic antidepressants. Not only would such a mechanism potentially allow for improved efficacy of behavioral reshaping, it further would also provide an answer to a critical limitation of ketamine use in MDD. The strong and fast responses rarely outlast a week after infusion, thus leaving patients either as depressed as initially or provoking continuous, long term treatment with a drug for which disadvantageous cognitive and morphological consequences have been reported (see review [62]). In response to such important caveats, augmentative use of NMDA antagonists in the framework of "opening plasticity windows" for psychotherapy would probably find its pace particularly in the early treatment phase, where rapid antidepressant action enables intense therapeutic work with promising neuroplastic effects of target brain circuits underlying specific behavior [114]. The combination with psychotherapy, optimized for exploitation of such pharmacologically opened doors, then may provide a crucial answer to the unresolved challenge to sustain the positive response towards

ketamine. Most generally speaking, glutamatergic modulation via agents such as ketamine benefit psychotherapy via improved mood and boosting plasticity as early as 24 hours after single infusion – while psychotherapeutic learning is necessary to sustain this otherwise transient clinical improvement by behavioral readaptation which itself would be beyond any pharmacological intervention.

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