Synaptic Modulation in the Effect of Ketamine

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Abstract Our central nervous system constantly instructs movements, generates recognition, and calculates value and emotion. Constant adaptation to the environment may be achieved by the integration of emotion/reward and recognition. Some diseases of mind may come from failure in making integration adaptive to environment. Neuronal circuits are established by the experience-dependent synaptic plasticity of glutamatergic neurons. Many of such main routes are equipped with the recurrent inhibition by GABAergic interneurons and regulated by monoaminergic modulation representing the reward and emotion. Major depression disease is considered as a state of dysfunction of these circuits which is here referred to as maladaptation. Studies of antidepressant mechanisms of ketamine include how stress induces changes in the original circuit, and how ketamine achieves the recovery of its function. In this chapter both lines of studies are discussed from the view points of the excitatory synapse hypothesis of major depression, and mechanisms of transient and persistent synaptic plasticity including reconsolidation and extinction learning.

Keywords Ketamine · Enantiomers · Hydroxynorketamine · NMDA receptor · Neuronal circuit · Synaptic plasticity · Maladaptation · Associativity · BDNF

1 Introduction

This chapter briefly introduces molecular and cellular mechanisms of persistent memory to discuss their possible involvement in major depression disease (MDD), and antidepressant actions of ketamine and its related compounds including metabolites.

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1.1 Ketamine as a Unique Antidepressant

Ketamine has been known as a dissociative anesthetic and an analgesic (Tyler et al. 2017). As a psychotomimetic drug, ketamine elicits both positive and negative symptoms which bear close resemblance to schizophrenia (Krystal et al. 1994). Now ketamine is attracting significant attention as a unique antidepressant in many aspects (Berman et al. 2000). First, ketamine shows rapid and persistent effects as an antidepressant. Remission appears in MDD patients within 2 h after intravenous injection of ketamine and lasts for a week (Zarate et al. 2006). Second, ketamine has wider therapeutic effects on mood disorders. It alleviates refractory MDD which does not respond to conventional antidepressants such as SSRIs (Zarate et al. 2006). It also reduces suicidal thought (Wilkinson et al. 2018) and is effective also on bipolar disease (Diazgranados et al. 2010). Extensive efforts have been made to understand the mechanisms underlying the antidepressant effect of ketamine, which will lead us to invent a better antidepressant without aversive effects of ketamine. The rapid and persistent effect implies that ketamine attacks the center of the neuronal mechanisms by which depressive symptoms are produced. Studies further found that ketamine enhanced synaptic plasticity which is associated with expression of brain-derived neurotrophic factor (BDNF), another compound known to suppress depression (Shirayama et al. 2002). Recently, it was found that (2*R*,6*R*)-hydroxynorketamine (HNK), one of the ketamine metabolites, has the antidepressant effect like ketamine (Zanos et al. 2016, 2017; Suzuki et al. 2017). (R)-HNK at antidepressant-relevant concentrations did not affect N-methyl-D-aspartate (NMDA) receptor currents (Suzuki et al. 2017; Zanos et al. 2017), indicating that ketamine interacts with unknown target molecules other than NMDA receptors to show antidepressant effects.

1.2 Antidepressant Actions of Ketamine and Circuit Behaviors

Ketamine is known as a noncompetitive antagonist of the NMDA-type of glutamate receptors (Anis et al. 1983). NMDA receptor plays pivotal roles in synaptic plasticity (Collingridge et al. 1983), which is the central mechanism underlying experience-dependent establishment and maintenance of neuronal circuits in the brain (Neves et al. 2008). Because ketamine blocks NMDA receptor, it is likely that ketamine blocks plastic changes in glutamatergic synapses. However, it is reported that ketamine facilitates long-term potentiation (LTP), a typical mode of synaptic plasticity associated with sustained enhancement of synaptic transmission. Ketamine enhances responses of α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors, another and the major glutamate receptors that generate excitatory postsynaptic potentials. In addition, ketamine induces the expression of BDNF, which happens in persistent LTP (Autry et al. 2011). Furthermore, ketamine administration enhanced gamma wave oscillation, a phasic brain activity enhanced during higher brain functions (Nugent et al. 2018). These observations collectively

indicate that ketamine elicits the activation of neuronal connection through LTP-like enhancement of glutamatergic synapses.

1.3 Reconsolidation and Excitatory Synapse Hypothesis

Synaptic plasticity has been studied as a cellular basis of activity-dependent formation and maintenance of neuronal circuit (Bliss and Lømo 1973). Among higher functions of the brain, memory can be tested through behavioral tests in human and laboratory animals. LTP is currently considered as the cellular basis of establishment and maintenance of memory.

Episodic memory is memories of everyday life events, including context such as space, time order, persons and objects, and novelty, and generated in the hippocampus. Simultaneously, emotional values are calculated in another limbic structure, the amygdale. Episodic memory is acquired by experience, and its retention periods are related to the strength of the emotional impact or attention during experience. The strong memory is "consolidated" after the acquisition and can be recalled long after the experience (consolidation of the memory) (Wang and Morris 2010).

When the second experience results in a similar consequence to the first, the memory is enhanced. This reconsolidation is a mechanism of maintenance and even reinforcement of the original memory after recall (Wang and Morris 2010). On the other hand, when the second experience results in a different consequence from the first, recall of the memory of the first experience is inhibited. Sometimes a new memory is built for the second experience (Phelps et al. 2004). This is extinction learning. Aversive memories can be reduced by facilitating extinction learning or inhibition of reconsolidation (Lee et al. 2006; Shiller et al. 2010).

The excitatory synapse hypothesis of MDD (Thompson et al. 2015) considers the possibility that glutamatergic synapses in the corticomesolimbic reward circuit are affected by chronic stress. This system includes dopaminergic and serotonergic modulation of glutamate outputs, in accordance with the effects of many antidepressant drugs. However, this idea by itself does not explain the long-lasting effect of ketamine, which is a characteristic advantage of ketamine. Memory mechanisms based on the synaptic plasticity and reconsolidation may explain MDD as learned maladaptation of the neuronal circuits representing emotion and memory.

Plasticity-dependent maladaptive circuit hypothesis (Fig. 1) may suggest mechanisms of ketamine action. When experience is modest, synaptic plasticity makes the neuronal circuit functions adapted to the environments (Fig. 1a), while successive stressful experience modulates monoaminergic transmission and generates maladaptation of neuronal circuit (Fig. 1b). Ketamine blocks the activity of the malfunctioning circuit by interacting with NMDA receptor or other target molecules. Also, ketamine is considered to elicit a sustained recovery of the healthy behaviors through a revival of the original, adapted circuit or the activation of substituting circuits (Fig. 1c). Antidepressants having affinity to glutamatergic circuits such as ketamine may inhibit reconsolidation and reduces reinforcement effects of

continuous stress. Alternatively, they may facilitate extinction learning. The reward circuit may be the major target, but it includes multiple regions such as the medial prefrontal cortex, the hippocampus, the nucleus accumbens, the ventral tegmental area, the amygdala, and the lateral habenula. Furthermore,multiple targets for the antidepressant action of ketamine (Zanos et al. 2016) are suggested. To evaluate the hypothesis, region and target molecules of ketamine action should be specified.

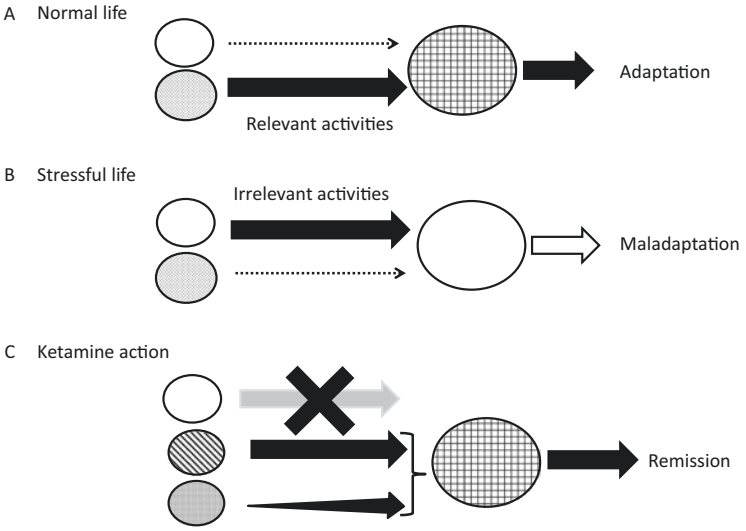

Fig. 1 Plasticity-dependent maladaptive circuit hypothesis. (a) Sensory inputs from environments and internal conditions in ordinary everyday life (shaded circle at the left) usually establish (thick arrow) adaptive neuronal circuits (meshed circle in center) through persistent plasticity. Unusual inputs (open circle at the left) usually fail to establish its circuit (dotted arrow). (b) Stress may give different types of inputs to the neurons which cause transient changes in behaviors. Prolonged or recursive stressful life generates persistent plasticity probably through activation of the monoamine modulatory inputs of the reward and emotional systems (thick arrow). The neuronal circuit specifically responding to robust but rare inputs will be established; however, it is not adaptive to usual environment (open arrow). In MDD, normal adaptive circuit may be masked (dotted arrow). (c) Ketamine is supposed to have two effects on the maladaptive circuits. First, sensory integration involving irrelevant signals, which is dominant in MDD, is inhibited by effects of ketamine (a cross on thin arrow) by means of transient disruption of transmission or inhibition of reconsolidation of the irrelevant circuit. Second, the adaptive circuit is restored by BDNF-dependent LTP. Two ways of restoration are considered. Case 1 is substitution (thick arrow from hatched circle that is representative of alternative adaptive conditions, at the left), which is achieved by establishment of a distinct link between sensory and integration systems by consolidation. Case 2 is revival (growing arrow from shaded circle), which is achieved by reactivation of the original adaptive circuit by extinction learning. Both possibilities suggest that the ketamine action should be long lasting to complete the remission. To make appropriate LTP, the context recognition of the patient should be supported, for example by association of occupational therapy

2 Persistent Synaptic Plasticity, Consolidation and Reconsolidation of Memory

Here, I summarize molecular and cellular mechanisms of synaptic plasticity, which may be critically involved in antidepressant effects of ketamine.

2.1 Synaptic Plasticity and Neuronal Circuit Formation

Brain functions are executed by neuronal circuits in which neurons are connected by synapses. Presynaptic release of neurotransmitters depolarizes (EPSP) or hyperpolarizes (IPSP) the postsynaptic cell by binding to postsynaptic receptors. Amplitude of postsynaptic potentials is variable (graded). When the depolarization at the initial segment of the postsynaptic axon exceeds the threshold, action potentials are evoked (firing), by which the excitation of the postsynaptic cell is transferred to the next cells. Thus, a neuronal circuit is composed of neurons linked to each other by dominant synapses which frequently contribute to firing of the postsynaptic cells.

Observation of unitary transmission revealed that principal neurons in the central nervous system (CNS) often fail to evoke EPSP, suggesting that the transmission has low efficiency. Furthermore, among many EPSP-evoking events, a limited number of EPSP can contribute to generate action potentials. How a synapse becomes dominant? Efficacy of synaptic transmission is regulated by several mechanisms, among which use-dependent plasticity is a mechanism that allows the circuit to behave in a manner adaptive to the environment. Hebb (1949) proposed a hypothesis in which functional neuronal circuits are established by a rule of "win for the used." Namely, a synapse may be dominant and survive if its activity frequently contributes to postsynaptic firing. Each of the principal neurons in the brain, such as pyramidal cells in the cerebral cortices, has tens of thousands of synapses receiving distinct presynaptic fibers carrying distinct activities from a variety of precedent neurons. Dominant synapse selectively carries one of such activities that frequently happen in the given environment. Synaptic plasticity is a mechanism by which dominant synapses are made in an activity-dependent manner. Plastic modulation of projection neurons is likely to contribute in making functional connections between distant brain areas.

Another possible role of plasticity may be the association. One neuron receives multiple input signals at different synapses which are mutually independent, while a neuron has only one output axon. Therefore, a single neuron can participate in multiple lines of signals through different synapses. This may cause the association of distinct events. Association of memory may be important to construct the abstract and collective concepts, our intelligence, and even our personality. Although these considerations are not supported by experimental evidence, we can imagine that if such an association accidentally takes place among irrelevant experiences, the brain

recognizes the experience, or environment, with irrelevant value. In this chapter, maladaptation of neuronal circuit means misassociation between signals in the reward system which leads to dysfunction of the system.

2.2 Synaptic Plasticity

LTP was found by Bliss and Lømo (1973) in perforant path/granule cell synapses in the rabbit dentate gyrus and seemed to conform to Hebb's hypothesis. The LTP establishment includes presynaptic, postsynaptic, and perisynaptic mechanisms, and a dominant mechanism governing the LTP seems to differ between synapses. LTP in the hippocampal CA1 pyramidal cell/Schaffer collateral synapses as well as the dentate gyrus granule cell/perforant path synapses occurs predominantly under the postsynaptic mechanisms. LTD (long-term depression, a plastic decrease of synaptic transmission) in Purkinje cell/parallel fiber synapse occurs also by the postsynaptic mechanism. In contrast, LTP in the hippocampal CA3 pyramidal cell/mossy fiber synapse occurs predominantly under the presynaptic mechanism. It is noted that synaptic efficacy can be altered by changes in every one of the residents of synapses, such as transmitter availability, exocytosis kinetics, synaptic cleft geometry, availability and sensitivity of postsynaptic receptors, and excitability. Research with superresolution microscopy revealed that presynaptic and postsynaptic machinery are allocated so that transmission occurs effectively. For instance, presynaptic centers of exocytosis and postsynaptic receptor scaffolding proteins are localized face-to-face in the synaptic membranes (Sakamoto et al. 2018).

Although LTP was found in vivo experiments, its molecular mechanisms were revealed mainly by electrophysiological and cell biological experiments using acute brain slices. Transient, short-term LTP was evoked in CA1 of hippocampal slices by electrical stimulation of presynaptic axons at 100 Hz for 1 s (for example Okada et al. 1989). Spike-timing dependent plasticity in the cerebral cortex was usually evoked by brief depolarization of postsynaptic cell together with weak activation of presynaptic axon (Markram et al. 1997). In CA1 and dentate synapses, these stimuli activate NMDA receptor, which resulted in an increase in the number of AMPA-type glutamate receptors (functional plasticity), mainly GluA1 subunits, expressed in postsynaptic plasma membranes (surface expression) (Shi et al. 2001). It is associated with spine head enlargement by actin filament polymerization (morphological plasticity) (Matsuzaki et al. 2004). LTD in this synapse is a persistent decrease in EPSP amplitude and spine shrinkage (Zhou et al. 2004). LTD is a distinct type of plasticity and should be discriminated from depotentiation which is a counterreaction of LTP (Malenka and Bear 2004). These changes are regulated by the kinase cascade reactions, including calcium-calmodulin-dependent kinases (CaMKs) and mitogen-activated protein kinases (MAPKs) (Thomas and Huganir 2004). The effects of protein phosphorylation are reversible due to dephosphorylation and ubiquitin-dependent degradation of the protein (Jouvenceau et al. 2003). Thus, the expression of short-term LTP depends on phosphorylation of preexisting synaptic

proteins. It is reversible and referred to as transient LTP. Expression mechanisms of LTP/LTD differ among synapses. For example, the reduction in spine head diameter is not observed in LTD of cerebellar Purkinje cell/parallel fiber synapses (Sdrulla and Linden 2010).

2.3 Molecular and Cellular Mechanisms of the Transient LTP

Establishment of transient LTP has three important characteristics: cooperativity, input-specificity, and associativity. Studies of the molecular mechanisms of LTP revealed relevance of these features in memory.

1. Cooperativity: Strong input is required for LTP establishment.

   Strong input is supplied by repetitive activity at high frequency of the presynaptic cell or robust depolarization of postsynaptic cell by activity of a second presynaptic axon. Sensory system always receives signals from the outer world and conditions of the body. Therefore, if LTP arises from tiny excitation of neurons, our sensation may be filled up with noise. Synaptic plasticity with cooperativity guarantees the stable and contrasted sensation, which may be advantageous for adaptive behaviors.

   The magnitude of Ca^{2+} influx (peak and duration) is an essential determinant for direction of the plastic change (Mizuno et al. 2001), suggesting that the cooperativity of LTP is regulated by intracellular Ca^{2+} concentrations (Malenka et al. 1988). The spike timing-dependent plasticity protocol revealed that higher intracellular Ca^{2+} concentrations lead to LTP, while LTD appears in lower Ca^{2+} concentrations (Dan and Poo 2004).
2. Input specificity: LTP is established exclusively in the synapse which received inputs sufficient for the cooperativity.

   LTP in one synapse is known to activate surrounding synapses by diffusion of activated molecules (Hedrick and Yasuda 2017), which alters the sensitivity of the neighboring synapse for triggering plasticity, a phenomenon known as metaplasticity. However, in general, crosstalk between the original synapse and unrelated axons having distinct information is prevented by the input specificity mechanisms, so that the cooperative activity evokes LTP only in the selected synapses. The coincidence detection mechanisms such as the depolarization-induced release of Mg^{2+}-blockade of NMDA receptor is known as the input-specificity mechanisms of short-term plasticity (Tsien 2000). This mechanism evokes robust intracellular Ca^{2+} influx only when both pre- and postsynaptic cells are depolarized in CA1 pyramidal cells (Nowak et al. 1984). The postsynaptic Ca^{2+} increase evokes LTP which is confined in these synapses.

   Optogenetic experiments with genetically modified mice showed that the memory of the learned tasks was recalled by reactivation of synapses which had been activated during learning (training in experiments) (Liu et al. 2014), whereas specific ablation of the synapses that had been activated during training

selectively destroyed the memory of the learned task (Hayashi-Takagi et al. 2015). These results strongly support the synapse-dependent formation of neuronal circuit according to Hebb's hypothesis.

Input-specific LTP supports establishment of the input-relevant circuit. Failure in the input-specificity mechanism may cause dysfunction of the circuit. It is possible that the malfunction of input-specificity causes irrelevant coupling of unrelated experiences. This may cause erroneous or inadequate recognition. In MDD, confused association of thoughts or emotion may cause irregular thoughts characteristic of the patients.

3. Associativity: When robust depolarization and a weak input come to a neuron simultaneously, LTP appears in both synapses. The LTP evoked in weakly stimulated synapse in association with strong heterosynaptic activity is called associative LTP.

Associative plasticity is a cellular model of association memory. Behavioral experiments indicate that associative memory is formed by training using combinatorial stimuli, a learning protocol known as classical conditioning. Consider that the "stimulus A" evokes the "behavior A", while the "stimulus B" evokes the "behavior B". Importantly, the "stimulus A" does not evoke the "behavior B" by itself. When both "stimulus A" and "stimulus B" are given simultaneously, the animal sometimes learns the connection between two stimuli and then the "stimulus A" becomes to evoke the "behavior B". In psychological protocol of the conditioned learning, "stimulus A" is the conditioned stimulus, and "stimulus B" is the unconditioned stimulus.

To make an associative memory, it is assumed that the synapse commonly activated by both stimuli A and B should be generated in a neuron participating in the circuit. Such common synapses are referred to as behavioral tag (Ballarini et al. 2009; Nomoto et al. 2016). Recent study demonstrated that the association of false memory can be artificially established, suggesting that the behavioral tag associated two behaviours (Ohkawa et al. 2015). The behavioral tagging mechanism suggests a hypothesis for MDD, in which the maladaptive neuronal circuit is formed by irrelevant selection of association pair. Continuous experience of extreme life events or hard environments may affect emotional circuits which in turn enhance plasticity to form the behavioral tag in irrelevant synapse leading to maladaptive behaviors.

2.4 Consolidation of Episodic Memory and Its Molecular Components

Synaptic plasticity has the possibility to be a major mechanism to establish maladaptive neuronal circuit that can be related to MDD. Although transient LTP or LTD is reversible, the MDD pathology is long lasting, suggesting that ketamine is likely to affect the persistent type of plasticity.

Long-lasting memory can be recalled by looking back long time after the initial experience. According to psychology of the memory, long-lasting memories are consolidated as a stable memory. In the words of neuronal cell biology, memory consolidation is establishment of a stable neuronal circuit, in other words, synaptic connections between neurons become stably robust. These neurons are reactivated synchronously by a cue input of a component of the episode, which is recall of the memory. Consolidation of memory is considered to be supported by persistent synaptic plasticity which requires the following four cellular events (Reymann and Frey 2007):

1. Transient plasticity: In the persistent LTP, both functional and morphological changes evoked in the transient LTP become persistent. Synaptic functions and structures are changed by transient LTP, which may work as the preparation for the persistent reforming of synapse by newly synthesized proteins (Inoue et al. 2007).
2. *de novo* protein synthesis: Persistent LTP requires induction of gene expression and is blocked by inhibitors of transcription and protein synthesis. Long-term memory requires reinforcement inputs such as dopamine transmission which activates cyclic AMP-responsive element (CRE)-dependent induction of transcription (Silva et al. 1998). Although the precise nature of reinforcement inputs is not clear, persistent LTP enhances CRE binding protein phosphorylation in the nucleus and new protein synthesis takes place in the soma and dendrites. Animal experiments reported that expression of about 800 genes was changed with various time lags according to genes (Ryan et al. 2012). Since newly synthesized protein is the critical for the persistent plasticity, cooperativity of persistent LTP is assigned to protein synthesis-evoking stimulus such as dopaminergic input.
3. Allocation mechanism of newly synthesized proteins: Newly synthesized proteins function only in the activated synapses. Following two mechanisms are known to manage this. These mechanisms support input-specificity of the persistent plasticity through localization of the newly synthesized proteins.

   "Synaptic tagging and capture" hypothesis assumes that the transient plasticity activates the "synaptic tag" in the activated synapses. A synaptic tag enables the newly synthesized synaptic proteins to function in the synapse to cause persistent plasticity (Frey and Morris 1997). This hypothesis assumes that the newly synthesized proteins in soma are unspecifically transported along most of dendrites, while these proteins function specifically in the synapse where the transient plasticity took place (Sajikumar and Frey 2004). Molecular mechanism of synaptic tagging for Homer-1a protein was unraveled (Okada et al. 2009). Protein trafficking is not free between dendritic spine and dendrite (Bloodgood and Sabatini 2005). Homer-1a protein is synthesized in soma, unspecifically transported in most dendrites, and then enters spines only where synaptic NMDA receptor is activated. Thus, the synaptic tag of Homer-1a protein is the activity-dependent regulation of spine entry of the protein. Synaptic tags are possibly variable depending on proteins.

Local synthesis is another allocation mechanism that supplies proteins such as Ark and GluA1, by translation in dendrites, at the gate of spines or within spines (Everwine et al. 2001). Local synthesis occurs in a mTORC-dependent manner, using preexisting translational machinery such as initiation and elongation factors and ribosomes (Schuman 1999). The dendritic transport of the mRNA of particular genes is the important component of local synthesis (Wang et al. 2009). AMPA receptors synthesized in the dendrites are incorporated in the synaptic plasma membranes (Ju et al. 2004). Experiments suggested that both local synthesis and synaptic tagging are necessary for persistent associative LTP and they are likely not mutually exclusive. Ryan et al. (2012) reported that changes in expression of over 800 genes were detected during 5 and 24 h after induction of persistent LTP in vivo, which shows different sets of genes are activated at different time, probably due to the cascade activation of transcription factors. Therefore, synaptic tagging and local synthesis may regulate allocation of distinct sets of gene products within the distinct time windows (Okada and Inokuchi 2015).

4. Reconstruction of the synapse: Persistent LTP enhances AMPA receptor-dependent current, spine head diameter, and postsynaptic density (PSD) size in a sustained manner. Newly synthesized proteins are localized in the activated synapses, and believed to reconstruct the molecular architecture of the synapse so that enhanced numbers of synaptic molecules may function stably. To reconstruct synaptic molecular complex, the existing complex is destroyed at first. This scrap-and-build process reforms the enlarged synapse, thereby achieving stable enhancement of synaptic function and morphology. For example, Homer-1c makes scaffolding networks in the PSD (Hayashi et al. 2009). Homer-1a is an immediate early gene activated in persistent LTP in the hippocampal CA1 and induces breakdown of the Homer-1c-dependent protein complex in the PSD, and this breakdown is necessary for building the enlarged Homer-1c complex (Inoue et al. 2007).

2.5 Recall and Reconsolidation of Episodic Memory

Neuronal circuit that supports an episodic memory is established by transient plasticity at the moment of experience. It is stabilized (consolidated) by persistent plasticity, which is associated with stable enlargement of postsynaptic protein complex. However, the memory recall by presentation of cues that remind the original experience is known to destroy the synaptic molecular complexes by ubiquitin-proteasome systems (Lee et al. 2008). Nevertheless, a second or a third presentation of the episode often succeeds recalling the memory, suggesting that the recall cue both destroys the consolidated synaptic complex and builds it again to hold the memory. In our everyday life, one can notice that a second memory often differs from the first impression. Actually, the molecular structure supporting the first memory is destroyed by recall and rebuilt anew by reconsolidation mechanism. Reconsolidation

of the hippocampal contextual memory involves activity in the cortex. Reconsolidation of the emotional memory obtained by conditioning in the amygdale is also regulated by the cortex. Reconsolidation is a memory updating process which enhances the original memory when a second experience is very similar to the first (Wang and Morris 2010).

When a second experience differs from the first in its emotion or reward, then the cortical activity masks the original memory circuit in the amygdala to prevent its reactivation. The memory circuit continue to exist but cannot be activated, while a new memory is generated according to the second consequence. Thus, this phenomenon is called extinction learning. The original memory often relapse depending on the magnitude of cortical inhibition. Extinction mechanisms involve many distinct brain structures such as hippocampus and prefrontal cortex, as well as nucleus accumbens for reward memory and amygdale for emotional memory. For example, infralimbic medial prefrontal cortex (ILmPFC) integrates memories and when a second experience does not involve emotional cue, ILmPFC inhibits amygdale output, resulting in extinction learning of amygdale memory (Quirk and Mueller 2008).

2.6 Modulation of Gamma Oscillation by Ketamine

Gamma wave is oscillatory activity at 30–90 Hz and attracts attention due to its relationship between higher brain functions such as memory. Changes in gamma wave oscillation are considered as the brain-wide activity representing depression. On the other hand, ketamine enhance both gamma power and AMPA receptor currents, suggesting the antidepressant effect of ketamine comes from LTP of the gamma oscillation producing pyramidal cells. Studies with mathematical models suggested that gamma wave requires the recurrent micro-circuit consisted of a pyramidal neuron which is recurrently inhibited by Parvalbumine-expressing basket cells (PVBCs) (Bartos et al. 2007). These microcircuits make pyramidal cells fire synchronously. The calcium-permeable GluA2-absent AMPA receptors are the dominant source of Ca^{2+} influx triggering neurotransmitter release from PVBC (Goldberg et al. 2003). Providing contribution of NMDA receptor is small, inhibition of NMDA receptors by ketamine in this circuit may not affect the gamma wave power (Gonzalez-Burgos and Lewis 2012). Thus, relationship between gamma wave and ketamine action is still not clear.

3 Possible Target Molecules of Ketamine

3.1 NMDA Receptors

Dizocilpin (MK801), phencyclidine, and ketamine are non-competitive antagonist of NMDA receptor channels. They are open channel blockers which enter the receptor's open pore to occlude it. MK801 is specific to NMDA receptor and irreversibly bind to it, while ketamine binding is low affinity (McDonald et al. 1991). Ketamine has dual effects toward excitatory and inhibitory synapses. NMDA receptor pore in neurons at resting potential is occupied by extracellular Mg^{2+} ions. Therefore, ketamine inhibits NMDA receptor only when it is open. It is likely that inhibition of NMDA receptors in excitatory postsynapses suppresses LTP.

NMDA receptors are tetrameric and composed of 2 subunits of GluN1 and 2 subunits of GluN2 or GluN3. Glutamate binds to GluN2 subunits, whereas GluN1 and GluN3 bind glycine and D-serine. GluN2 receptors have 4 isoforms, GluN2A, B, C and D. The affinity of ketamine for these receptors is nearly equal (Paoletti and Neyton 2007). However, NMDA receptors containing GluN2C or 2D elicit inward current by unitary glutamate transmission because their channels show weaker Mg^{2+}-blockade (Larsen et al. 2014). GluN2B/D-containing channels are expressed in the axonal terminals of the cerebellar stellate cells, which are inhibitory. GluN2B/D mediates spontaneous activity of these interneurons at resting potential, which is required for the long-term release of GABA (Dubois et al. 2016). Blockade of NMDA receptors with weak Mg^{2+}-blockade in the axon terminals of inhibitory neurons suppresses the output from resting neurons, causing disinhibition of the circuit (Akgül and McBain 2016). Neuronal circuits composed of a main output of glutamatergic principal neuron, recurrent GABAergic inhibitory neuron, and monoaminergic modulatory inputs are often seen in the brain as important role players for recognition and diseases (Carlen et al. 2012; Nakazawa et al. 2012; Ren et al. 2016). Experiments with knockout mice showed that antidepressant effect of (*R*)-ketamine required GluN2D receptor (Ide et al. 2017).

In the lateral habenula, NMDA receptor is involved in generation of bursting action potentials in inhibitory neurons such as PVBCs. This bursting is enhanced in MDD-like conditions (Yang et al. 2018a). Bursting activity of inhibitory PVBC strongly inhibits projection neurons and the downstream monoamine systems. Ketamine inhibits NMDA receptors, which blocks the bursting. It is noted that Kir4.1 channel expression is enhanced in MDD-like state (Cui et al. 2018). Increased expression of potassium channels causes depolarization of neurons by decreasing extracellular potassium concentrations, which is the cause of the NMDA receptor-dependent bursting of the neuron. After all, it seems that the mechanism of enhanced expression of Kir4.1 is critically linked to MDD pathology, but ketamine seems to inhibit MDD only transiently. Persistent antidepressant effect of ketamine may suggest involvement of plastic change in this circuit.

3.2 D-Serine and Other NMDA Receptor Ligands

Binding of co-agonists, D-serine, or glycine to the GluN1 subunit is prerequisite of glutamate-dependent activation of the receptor. Action of these co-agonists depends on the local extracellular concentrations. D-serine is synthesized by serine racemase (SR) in neurons. D-amino acid oxidase in astrocyte is responsible for its breakdown to pyruvate and hydrogen peroxide. D-serine is excreted to extracellular space through Asc-1 transporter. These molecules control extracellular D-serine concentrations. According to Papouin et al. (2012), NMDA receptors localized in pre- and post-synaptic membranes bind D-serine, while those localized in soma bind glycine. Decrease in extracellular D-serine attenuated LTP (Henneberger et al. 2010). D-serine interacts with other molecules such as cerebellar GluD2 and α7-nicotinic acetylcholine receptor (α7nAChR). α7nAChR increases SR expression through mTORC1 activation, while (*S*)-ketamine inhibits α7nAChR and reduces NMDA receptor activity (Paul et al. 2014).

Kynurenine is a tryptophan metabolite, and its derivative 4-chlorokynurenine is an NMDA receptor antagonist competitive with D-serine which is reported to show antidepressant effect (Zanos et al. 2015). An antibody against the glycine site, B6B21, has the partial agonist activity. Glyxins are peptides having amino acid sequences resembling the supervariable region of the antibody. Glyxin13 was delivered across the blood–brain barrier (BBB) and enhanced some forms of learning performance (Moskal et al. 2005).

MK801 and AZD6765 are open channel blockers of the NMDA receptor channel. MK801 showed specific and intense binding to NMDA receptors, while those of AZD6765 are weak. These drugs showed only transient antidepressant effects (Zarate et al. 2013; Maeng et al. 2008). By comparing this observation and the fact that ketamine, known to act at the same locus as MK801, shows persistent antidepressant effect, it is suggested that transient and long-lasting effects of ketamine may be resulted from multiple actions to different targets.

Ro25-6981 is a selective inhibitor of the GluN2B containing NMDA receptors. Its effects were not consistent between studies. Maeng et al. (2008) reported transient antidepressant effects, whereas Li et al. (2011) observed long-lasting effects although different behavioral tests were employed to estimate the antidepressant effects in these reports.

3.3 Enantiomers and Metabolites of Ketamine

Enantiomers and enantiomeric metabolites of ketamine are studied on the potency for use as antidepressant and results differ among studies (Ide and Ikeda 2018). Ketamine has high BBB permeability and its bioavailability is high when administered via intramuscular injection, but it is low via oral administration, suggesting that metabolic degradation in the liver is dominant (Ebert et al. 1997).

N-demethylation of ketamine gives norketamine, which in turn 6-hydroxylated to give 6-HNK. 6-HNK is also synthesized by 6-hydroxylation first followed by N-demethylation. Hydroxylation occurs also at 4- and 5-positions, but the major metabolite is 6-HNK. Ketamine has a racemic center at the second carbon, therefore consists of (*S*)- and (*R*)-enantiomers. Hydroxylation does not change the chirality; thus, (2*S*,6*S*)- and (2*S*,6*R*)-HNK are derived from (*S*)-ketamine and (2*R*,6*S*)- and (2*R*,6*R*)-HNK are derived from (*R*)-ketamine. Among these *cis–trans* isomers, the *cis* types are dominant; therefore, the major metabolites of (*S*)- and (*R*)-ketamine are (2*S*,6*S*)- and (2*R*,6*R*)-HNK, respectively (Zanos et al. 2016).

These metabolic reactions are carried out by cytochrome P450 (CYP). According to Tyler et al. (2017), N-demethylation involves CYP2A6, 2B4, 2C19, 3A4, and 3A5, while 6-hydroxylation of norketamine involves CYP2A6, 2B6, and 3A5. However, identification of the CYP isoforms involved in ketamine metabolism varied between studies, though CYP2A6 and 2B6 are reported as the common candidates. CYP has many isoforms and the variety differs among species. For example, the CYP2B6 gene is found in human, while it is absent in mice which have CYP2B1 as the highest homology. CYPs are expressed mainly in the liver, the adrenal gland, and the gonad glands. Some CYPs involved in estrogen synthesis (Hojo et al. 2004) and nicotine metabolism (Miskys et al. 2000) are found to function in the hippocampal neurons. Although HNK and ketamine readily cross BBB, ketamine was not metabolized in the rat brain homogenate, suggesting the major contribution of the liver CYPs in HNK production (Moaddel et al. 2016).

Some metabolites of ketamine are known to have antidepressant effects as well as psychomimetic effects. Ketamine and norketamine are NMDA receptor blockers and work as anesthetics and analgesics. (*S*)-compounds are 5 times more intense as an NMDA receptor blocker than (*R*)-compounds. *K*i values for each compounds for replacement of [^{3}H] MK-801 bound in rat brain membranes were: (*S*)-ketamine 0.3 μM vs. (*R*)-ketamine 1.4 μM, and (*S*)-norketamine 1.7 μM vs. (*R*)-norketamine 13 μM (Ebert et al. 1997). (*S*)-norketamine is more rapidly produced than (*R*)-norketamine.

Both enantiomers of ketamine are reported to have an antidepressant effect. Reus et al. (2015) reported that antidepressant effect of (*S*)-ketamine against the depression-like behaviors in the forced swimming test, the splash test, and the open-field test in adult rat received maternal deprivation. Zhang et al. (2014) reported, using juvenile mice received neonatal dexamethason exposure, acute antidepressant effect of both enantiomers of ketamine on the tail suspension test, the forced swimming test, and the sucrose preference test. Interestingly, they observed that (*R*)-ketamine selectively showed reduction in the immobility in the tail suspension and forced swimming tests 1 week after injection, suggesting (*R*)-ketamine has long-lasting antidepressant effects. These results suggest the possibility that the acute and long-lasting effects of ketamine were created by distinct enantiomers.

(2*R*,6*R*)-HNK, at lower concentrations than inhibiting NMDA receptor, was reported to show rapid and persistent antidepressant effects (Zanos et al. 2016, 2017). (2*R*,6*R*)-HNK raised the BDNF expression and the AMPA current enhancement in the hippocampus, suggesting that persistent LTP is established at least a

part. AMPA receptor currents are not enhanced by other NMDA receptor blockers. These results suggest that (2*R*,6*R*)-HNK elicits antidepressant effects through unknown target molecules other than NMDA receptors. Interestingly, Yang et al. (2018b) reported that (*S*)-norketamine showed more intense antidepressant effect against depressive behaviors induced by inflammation or chronic social defeat stress than (*R*)-norketamine. They also reported that (*R*)-ketamine but not (2*R*,6*R*)-HNK, had significant antidepressant effect.

These studies do not reach a complete agreement. Effects of these compounds should be tested using a common battery of behavioral test protocols. It is also important to note that these compounds have a distinct contribution on the acute and persistent antidepressant effects.

3.4 Raft and BDNF

Orser et al. (1997) suggested that ketamine affects NMDA receptors through two distinct mechanisms. One is filling in the open channel pore from the extracellular space and the other is having access to the receptor's allosteric site facing plasma membrane. The latter implies a possibility of ketamine action in the membrane. Wray et al. (2018) reported that in C6 glioma cells, ketamine treatment released Gαs proteins from lipid raft. Gαs activated adenylyl cyclase in the cell out of the raft and facilitated cyclic AMP-dependent events such as CRE-dependent BDNF expression. This response was not evoked by other NMDA receptor ligands, but (2*R*,6*R*)-HNK evoked similar response. They also showed that Gαs release from raft may involve tubulin acetylation. HDAC6 inhibition and knock out elicited antidepressant effects (Singh et al. 2018). This work suggests three independent possibilities. First, ketamine action does not necessarily require actions mediated by neurotransmitter receptors. Second, acetylation–deacetylation balance in the glial cells may be associated with cell biology of the depressed brains. Third, the ketamine targeted on the glia affects the nearby neurons through action of glia-derived BDNF.

Antidepressant effect of ketamine involves the synthesis and action of BDNF (Bramham and Messaoudi 2005). Observation of mTORC1 (Autry et al. 2011) and MAPK (Yang et al. 2018b) activation by ketamine support this idea. Loci of BDNF synthesis and action are ambiguous in these reports, while neuronal action of glia-derived BDNF is suggested (Wray et al. 2018). BDNF expression is the key step of persistent plasticity. CRE-dependent translation is triggered by binding of phosphorylated CREB protein onto the CRE (Malburg and Blendy 2005). Many protein kinases are reported to phosphorylate CREB, such as cyclic AMP-dependent protein kinase, CaMKII, GSK3β, Akt, and MAPKs. BDNF is released from the production cell by exocytosis. Plasma BDNF concentrations are low in MDD. Monoamine neurotransmitters facilitate LTP and BDNF production through CRE-dependent translation activation. BDNF production may be an important mechanism of antidepressant effects of SSRI. BDNF action is mediated by TrkB receptors, which in turn activates cascade reactions of kinases composed of MEK (a MAPK kinase), ERK (a

MAPK), and Akt. The MAPK cascade facilitates major expression mechanisms of LTP such as GluA1 trafficking and CRE-dependent transcription activation. Akt phosphorylation triggers mTORC1-dependent protein synthesis, which is involved in local protein synthesis.

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