The Mechanism of Memory Extinction

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Abstract

The memory of an event is encoded in an ensemble of "memory units", which are likely to be the dendritic branches, rather than individual synapses or spines. Thus, the membrane potential resulting from synchronous opening of NMDA receptors (NMDARs) in dendritic branches, known as NMDA spike or plateau, should make important contribution to the macroscopic state of a memory. This paper shows that the macroscopic memory of an event could be determined by the microscopic states of NMDARs involved in the generation of NMDA spike/plateau. Regarding memory extinction and retrieval, a GluN2B-containing NMDAR can have three distinct states: resting, open and extinction, but the extinction state does not exist in GluN2A-containing NMDARs because the tubulin/CRMP2 complex binds only to GluN2B, not GluN2A. Therefore, a large GluN2B/GluN2A ratio is prone to memory extinction. Sine BDNF promotes the localization of GluN2B-containing NMDARs to dendritic membrane, this explains why BDNF enhances extinction. Dopamine has also been shown to enhance extinction. Its underlying mechanism can be explained by the Tubulin Inhibition Hypothesis which posits that the memory extinction and retrieval are fundamentally governed by the competition between protein kinase A and calcineurin for the phosphorylation state of S1166 in GluN2B.

Introduction

The previous paper proposes that memory extinction and retrieval could be fundamentally governed by the interaction between tubulin/CRMP2 and NMDA receptors (NMDARs), which in turn is regulated by the competition

between protein kinase A (PKA) and calcineurin (CaN) for the phosphorylation state of S1166 located at the cytoplasmic domain of GluN2B (NR2B). Phosphorylation of S1166 by PKA facilitates retrieval whereas dephosphorylation of S1166 by CaN promotes extinction. Since the tubulin/CRMP2 complex binds only to GluN2B, not GluN2A, this hypothesis predicts that GluN2B is required for memory extinction, in agreement with experimental results (Sotres-Bayon et al., 2007; Dalton et al., 2012). Further details are described in this paper.

Spiny Neurons and Memory Storage

The memory of an event is stored in an ensemble of "memory units", which are likely to be the dendritic branches, rather than individual synapses or spines (Govindarajan et al., 2011). Several lines of evidence suggest further that memory could be stored in the dendritic branches of spiny neurons.

1. Spiny neurons are characterized by a large number of dendritic branches, well-suited for the storage of memory (Figure 1).
2. More than 90% of granule cells in the dentate gyrus are silent, which may result from memory extinction (Paper 15).
3. Spiny neurons could be the primary source of slow oscillations (Oikonomou et al., 2014), which have been demonstrated to orchestrate memory consolidation during sleep (Mölle and Born 2011).

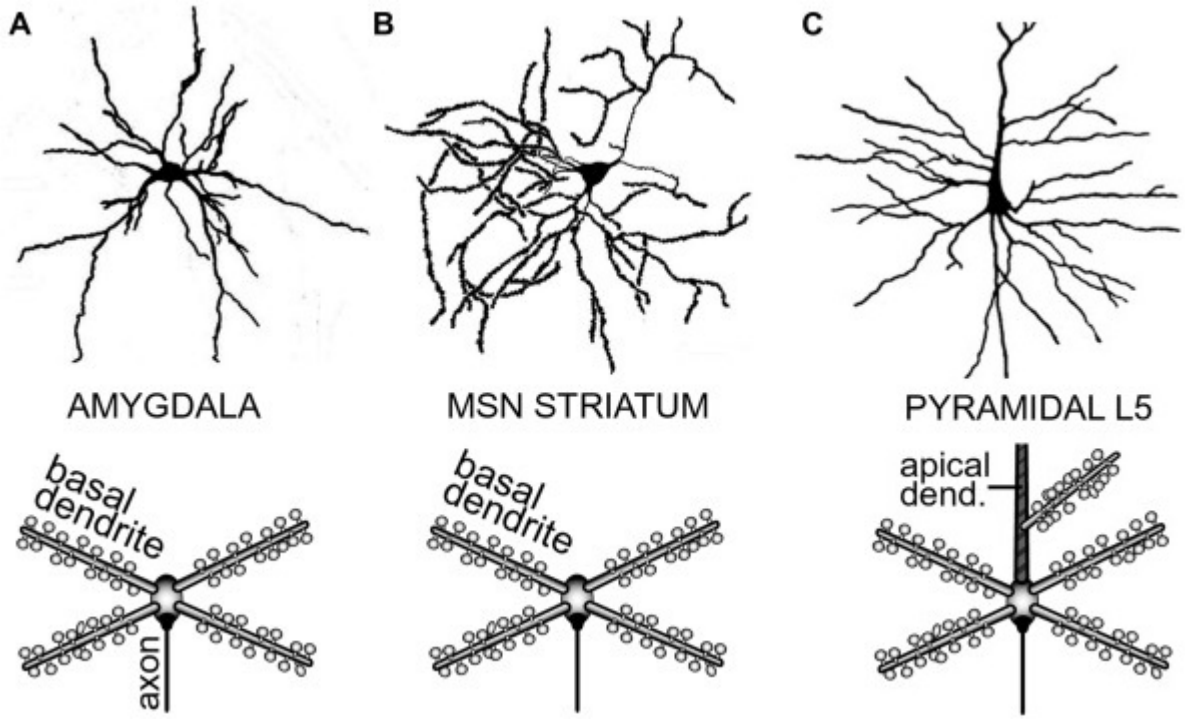

Figure 1. Examples of spiny neurons. The upper image is a camera lucida drawing, while the lower image is a conceptual representation of the dendritic tree. The granule cells of the dentate gyrus (not shown) may also be considered as spiny neurons. Pyramidal layer 5 (L5) neurons have been shown to initiate slow oscillations during sleep. [Source: Oikonomou et al., 2014]

The Role of NMDA Spike/Plateau in Neuronal Firing

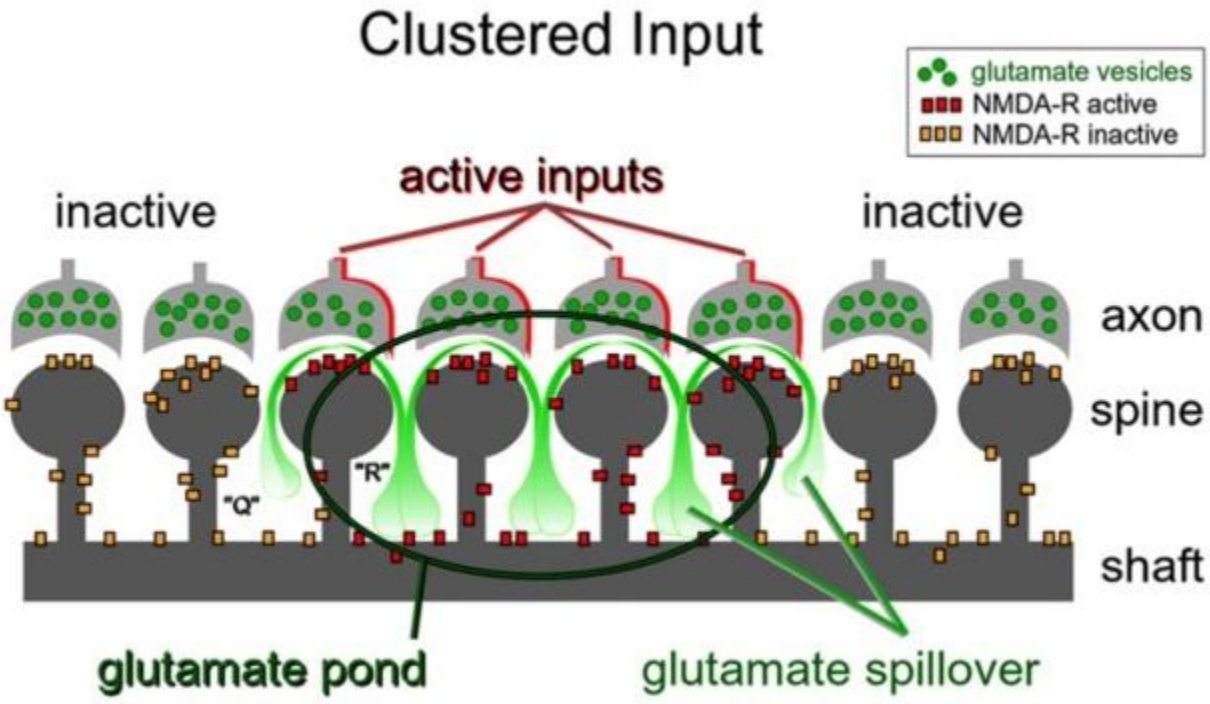

Figure 2. Distribution of NMDARs. Extrasynaptic NMDARs could be activated by glutamate spillover, making important contribution to NMDA spike/plateau. [Source: Oikonomou et al., 2014]

NMDARs are located not only at synapses, but also widely distributed in the extrasynaptic membrane (Figure 2). In particular, the spiny neurons of amygdala, striatum, and cerebral cortex are enriched with extrasynaptic NMDARs to produce NMDA spikes (Figure 3) and dendritic plateau potentials (Figure 4) that are crucial for the generation of action potentials in spiny neurons. Inhibition of these NMDARs by tubulin/CRMP2 could result in memory extinction.

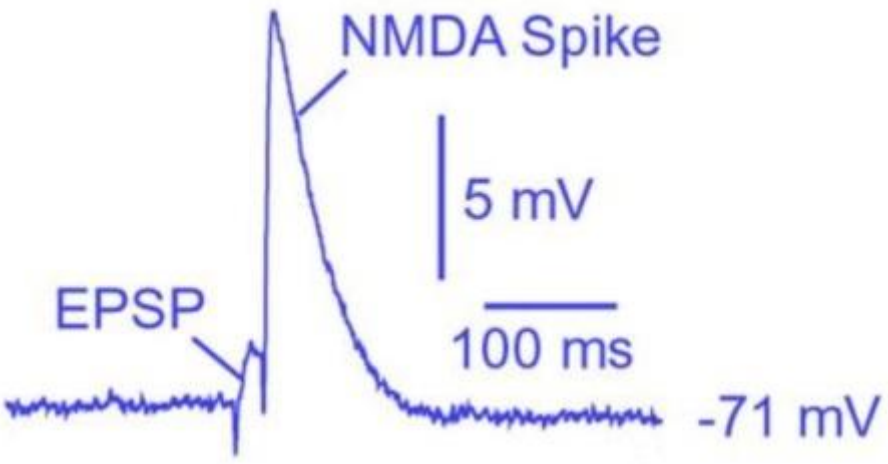

Figure 3. Comparison between excitatory postsynaptic potential (EPSP) and NMDA spike. [Source: Oikonomou et al., 2012]

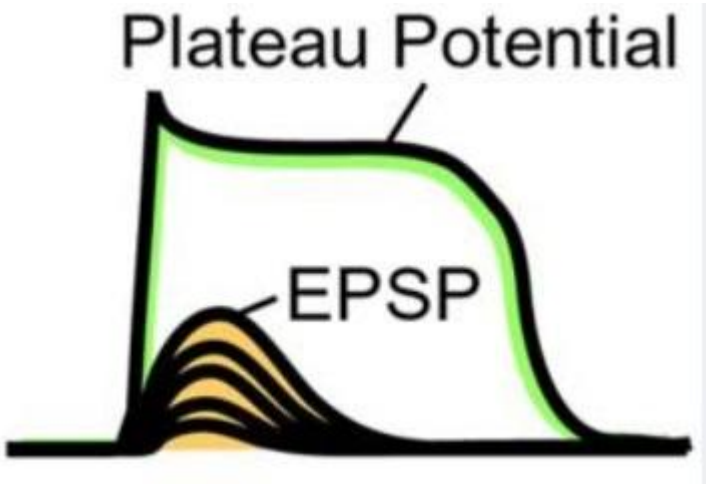

Figure 4. Illustration of the dendritic plateau potential (NMDA plateau). [Source: Oikonomou et al., 2014]

The NMDA spike is a membrane potential change arising from synchronous activation of 10-50 neighboring synapses that leads to the opening of NMDARs (Schiller et al., 2000; Antic et al., 2010; Chalifoux and Carter, 2011). A larger ensemble of NMDARs may produce the dendritic plateau potential, called "NMDA plateau". Since the amplitudes of NMDA spike and plateau are larger than EPSP, they make important contribution to the generation of action potentials. In layer 5 pyramidal neurons, it has been shown that the AMPAR-only EPSPs are too small to trigger neuronal firing. The

large amplitude of NMDA spikes in their basal dendrites is also required (Polsky et al., 2009). Hence, inhibition of these NMDARs by tubulin/CRMP2 may reduce the probability of neuronal firing, resulting in memory extinction. **The more NMDARs in the same branch are inhibited, the harder the memory encoded by this branch will be retrieved.**

Interestingly, compelling evidence has revealed that the slow oscillations are initiated by layer 5 pyramidal neurons (Lőrincz et al., 2015; Neske, 2016), consistent with the notion that the NMDA spike/plateau in the basal dendrites of these neurons could trigger slow oscillations during sleep (Oikonomou et al., 2014). Exactly how the NMDA spike/plateau is generated to initiate slow oscillations for consolidation will be discussed in Paper 23.

The Role of BDNF in Extinction

The brain-derived neurotrophic factor (BDNF) infused into the infralimbic cortex is capable of inducing fear extinction (Peters et al., 2010). Infusion of BDNF into the dorsal medial prefrontal cortex (mPFC) attenuates reinstatement to cocaine-seeking behavior (Berglind et al., 2009), suggesting that the memory of cocaine-induced pleasure could be suppressed by BDNF. Furthermore, hippocampal-specific deletion of the *BDNF* gene significantly reduced extinction of conditioned fear (Heldt et al., 2007). Therefore, BDNF in both mPFC and hippocampus has the capacity to cause memory extinction. Its underlying mechanism is discussed below.

The macroscopic memory extinction is a combined result of microscopic states represented by NMDARs that give rise to NMDA spike/plateau. Regarding memory extinction and retrieval, a GluN2B-containing NMDAR can have three distinct states (see Paper 19).

1. **The resting state:** The channel is closed by Mg^{2+} block and intrinsic gate; S1166 of GluN2B is phosphorylated by PKA, preventing NMDAR inhibition by tubulin.

2. **The open state:** The intrinsic gate is open (regulated by glutamate binding) and the Mg^{2+} block is relieved (regulated by electric fields).
3. **The extinction state:** S1166 is dephosphorylated, allowing tubulin binding to GluN2B, thereby hindering Mg^{2+} relief. The channel is closed regardless of the intrinsic gate.

The GluN2A-containing NMDAR does not have the extinction state, because the tubulin/CRMP2 complex binds only to GluN2B, not GluN2A. Therefore, the macroscopic memory extinction should depend on the GluN2B/GluN2A ratio in the dendritic branches that encode the memory. A large GluN2B/GluN2A ratio is prone to memory extinction.

In the cytoplasmic domain of the GluN2B subunit, there are three tyrosine residues (abbreviated as Y) which can be phosphorylated by Fyn or Src kinase. Phosphorylation of Y1472 prevents GluN2B-containing NMDARs from being internalized (Chen and Roche, 2007), consequently increasing their localization to the membrane. The membrane-bound GluN2B-containing NMDARs are subject to tubulin inhibition, which would suppress NMDA spike/plateau, leading to memory extinction. BDNF has been shown to promote Y1472 phosphorylation (Xu et al., 2006), possibly via the BDNF/TrkB/Akt/Girdin/Src pathway (Nakai et al., 2014). This notion is supported by the finding that the Src family kinases are involved in the BDNF-mediated suppression of cocaine-seeking (Barry and McGinty, 2017).

Tet1 also plays an important role in memory extinction (Rudenko et al., 2013), but its actions could be mediated by BDNF. Tet1 is an enzyme that promotes DNA demethylation which is often used to regulate gene expression. Tet1 has been demonstrated to regulate the expression of the *BDNF* gene (Hsieh et al., 2016; Keifer, 2017).

This mechanism is further supported by the finding that vorinostat, a histone deacetylase inhibitor, facilitates fear extinction by enhancing the expression of the hippocampal GluN2B (NR2B) gene (Fujita et al., 2012).

The Role of Dopamine in Extinction

Dopamine has at least five receptor subtypes, designated as D1 - D5. They all belong to G protein-coupled receptors. In most reports, activation of either D1 or D2 receptor by dopamine enhanced memory extinction (Abraham et al., 2014; Abraham et al., 2016; Mueller et al., 2010). Unlike BDNF, dopamine does not seem to enhance extinction by increasing the GluN2B level. Rather, it may activate its receptors to regulate the activities of PKA and CaN.

The activation of D1 receptors stimulates two different pathways, depending on the coupled G proteins. One of them involves adenylate cyclase (AC) and PKA; the other triggers the phospholipase C (PLC)/Ca^{2+} cascade. The D2 receptor stimulates the PLC/Ca^{2+} pathway, but inhibits the AC/PKA pathway (Abraham et al., 2014, Figure 1). As mentioned in Paper 19, the elevated Ca^{2+} level can activate the AC subtype 1 to increase PKA activity. It can also enhance the CaN activity. However, because D2 inhibits the AC/PKA pathway, its overall effects should be the enhancement of CaN, which according to the present model, should promote memory extinction.

The effects of D1 is more complex, as it may increase the activities of both PKA and CaN - the two competing enzymes for the phosphorylation state of S1166 in GluN2B. Recalling that the basal level of PKA is sufficient to phosphorylate S1166 in most GluN2B-containing NMDARs (Paper 19), the enhancement of PKA activity should have little impact on memory extinction. Therefore, the D1-mediated extinction may result from S1166 dephosphorylation by CaN via the PLC/Ca^{2+} pathway. This interpretation is corroborate by the finding that a cAMP/PKA biased D1 agonist (SKF 83959) did not affect fear extinction, whereas a broadly efficacious D1 agonist (SKF 83822) promoted fear extinction (Abraham et al., 2016).