The CABT Hypothesis of Schizophrenia

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Abstract

Decades of intensive investigations have revealed that the hypofunction of NMDA receptors (NMDARs) could be the convergence point for progression and symptoms of schizophrenia. On the other hand, compelling evidence suggests that schizophrenia could originate from elevated GluN2B/GluN2A ratio in the postsynaptic membrane. The CABT Hypothesis may provide the missing link between GluN2B/GluN2A elevation and NMDAR hypofunction. This hypothesis posits that NMDARs could be blocked by the CABT complex, which consists of a **C**RMP2 monomer, an **a**lpha and a **b**eta **t**ubulin. Both CRMP2 and tubulin have been shown to interact with the GluN2B subunit of NMDARs, but not GluN2A. Therefore, the CABT complex can block only GluN2B-containing NMDARs, without affecting GluN2A-NMDARs. This explains why GluN2B/GluN2A elevation may cause NMDAR hypofunction.

Glycogen synthase kinase 3 (GSK-3) is the convergent target of most antipsychotics. It has a plethora of substrates. Which one is critical for the regulation of NMDAR functions remains unclear. In the dendritic spine, CABT may bind either filamenous actin (F-actin) or GluN2B. Binding of CABT to F-actin would not block NMDAR currents. However, if F-actin is depolymerized, CABT would be forced to bind and block GluN2B-NMDARs. The activity-regulated cytoskeletal-associated (Arc) protein is known to prevent F-actin depolymerization. Strikingly, a recent study demonstrates that GSK-3 promotes Arc degradation. The CABT Hypothesis suggests that Arc could be the long-sought target of GSK-3.

Introduction

Schizophrenia is a mental disorder characterized by positive (hallucinations, delusions), negative (anhedonia, avolition) and cognitive symptoms. The cognitive symptoms may appear in early childhood, and often precede the development of positive (psychotic) symptoms in adolescence (Tamminga et al., 1998; Bowie and Harvey, 2006). Decades of intensive investigations have revealed that the hypofunction of NMDA receptors (NMDARs) could be the convergence point for progression and symptoms of schizophrenia (Olney et al., 1999; Kantrowitz and Javitt, 2010; Snyder and Gao, 2013). This paper will present evidence to corroborate this hypothesis and further propose that the NMDAR hypofunction could arise from the occlusion of GluN2B-containing NMDARs by the **CABT complex** which consists of a **C**RMP2 monomer, an **a**lpha and a **b**eta **t**ubulin. The occlusion could be regulated by the convergent targets of most antipsychotics: protein kinase A (PKA) and glycogen synthase kinase 3 (GSK-3) (Beaulieu, 2012).

The NMDAR Hypofunction Hypothesis of Schizophrenia

The NMDAR Hypofunction Hypothesis stems from the findings that the NMDAR blockers, phencyclidine and ketamine, can induce a broad range of schizophrenia-like symptoms (Jentsch and Roth, 1999). Before the advent of the NMDAR Hypofunction Hypothesis, theories for the pathogenesis of schizophrenia were dominated by the Dopamine Hypothesis (Davis et al., 1991), which posits that the cognitive and negative symptoms of schizophrenia were caused by reduced activity of dopamine in the prefrontal cortex while the positive symptoms result from hyperactivity of dopamine in the striatum. As shown in Figure 1, the Dopamine Hypothesis is actually a consequence of the NMDAR Hypofunction Hypothesis.

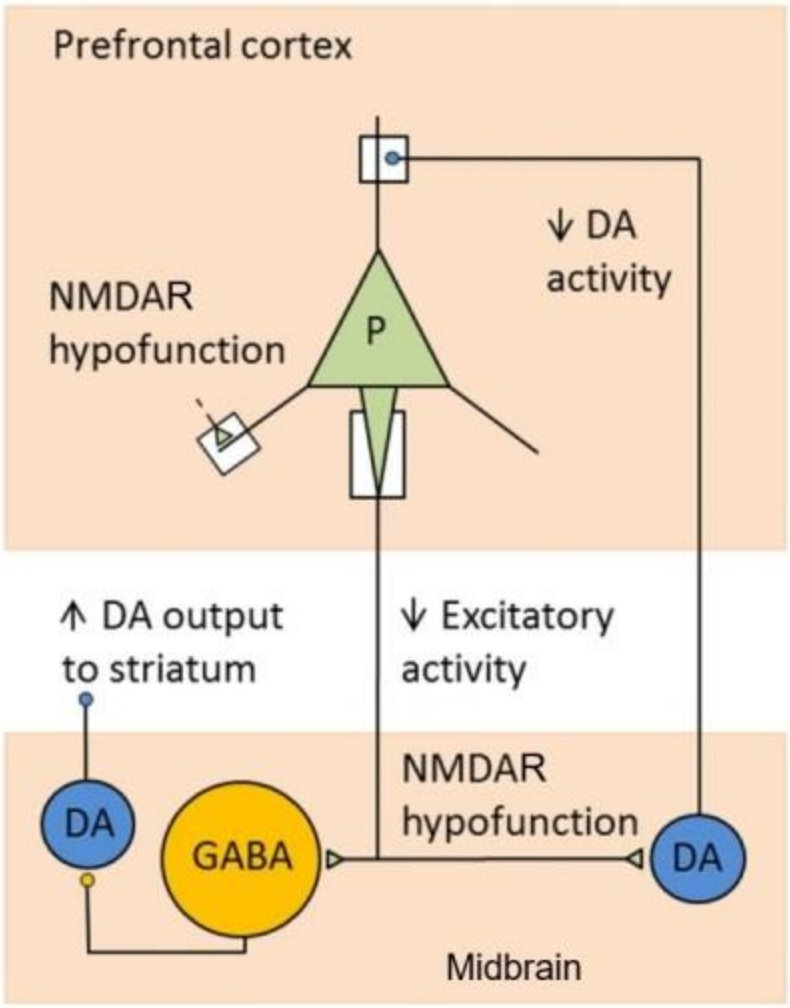

Figure 1. The dopamine (DA) abnormality postulated in Dopamine Hypothesis is a consequence of NMDAR hypofunction. NMDAR hypofunction in prefrontal pyramidal cells leads to decreased activity of DA neurons in the midbrain. This results in reduced DA release to the prefrontal cortex. However, it increases DA output to the striatum as a consequence of attenuated stimulation of GABA interneurons. [Source: Gruber et al., 2014]

What causes NMDAR hypofunction in schizophrenic patients? An NMDAR consists of two obligatory GluN1 (formerly NR1) subunits and two other subunits which, in adults, are mostly GluN2A (NR2A) and GluN2B (NR2B). Some NMDARs may contain GluN2C, GluN2D or GluN3 subunits. It was thought that the NMDAR hypofunction might originate from deficiency in NMDARs. Since GluN1 is the obligatory subunits, researchers have tested this notion by genetically knocking out GluN1 globally or in specific brain areas. As expected, the GluN1 knockout did cause schizophrenia-like symptoms (Nakazawa et al., 2017). However, this does not imply that natural

development of schizophrenia involves the lack of GluN1. As mentioned above, ketamine can induce a broad range of schizophrenia-like symptoms. Ketamine has been demonstrated to **increase** both GluN2B (Burgdorf et al., 2013) and GluN1 (Liu et al., 2013), but not GluN2A (Jeevakumar and Kroener, 2016).

The following sections will show that, in the majority of cases, schizophrenia could originate from elevated GluN2B/GluN2A ratio in the postsynaptic membrane, rather than lack of synaptic NMDARs.

Elevated GluN2B/GluN2A Ratio in Schizophrenia

At birth, NMDARs comprise predominately GluN2B, which is then progressively replaced by GluN2A during postnatal development (Quinlan et al., 1999). The GluN2B-GluN2A switch occurs in the period coincident with the progression of schizophrenia from early childhood to adolescence. Males are more commonly affected by this disorder and exhibit psychotic symptoms earlier than females (Aleman et al., 2003; Loranger, 1984). As predicted, males display higher GluN2B/GluN2A ratio than females (Sinclair et al., 2016). Aripiprazole, a third-generation antipsychotic, has been demonstrated to reduce the GluN2B/GluN2A ratio (Segnitz et al., 2011).

Mechanistically, the GluN2B-GluN2A switch is regulated primarily by repressor element-1 silencing transcription factor (REST), casein kinase 2 (CK2) and tyrosine kinase Fyn:

- REST is a transcription repressor. During normal postnatal development, REST is activated and triggers experience–dependent chromatin remodeling that represses the transcription of *grin2b*, the gene encoding GluN2B (Tamminga and Zukin, 2015; Rodenas-Ruano et al., 2012). Consequently, activation of REST should reduce GluN2B level. Adverse experience in early childhood may disrupt REST activation, resulting in higher GluN2B level (Tamminga and Zukin, 2015). In schizophrenia, the GluN2B-containing NMDARs have been found to increase in the hippocampal CA3 region (Li et al., 2015).
- CK2 regulates the postsynaptic localization of GluN2B-containing NMDARs by phosphorylating GluN2B at serine 1480 (S1480), which is in the binding domain of PSD-95 that anchors GluN2B-NMDARs to the postsynaptic membrane. Phosphorylation of GluN2B by CK2 will disrupt their binding, leading to endocytosis. Consequently, CK2 should reduce synaptic GluN2B-NMDARs (Chung et al., 2004; Sanz-Clemente et al., 2010). In schizophrenia, the CK2 level is decreased (Aksenova et al., 1991), consistent with the notion that excess synaptic GluN2B could lead to schizophrenia. *CSNK2B*, which encodes the β-

regulatory subunit of CK2, has been shown to be a risk gene for schizophrenia (Yang et al., 2018; Yoshikawa et al., 2018).

- While phosphorylation of GluN2B at S1480 promotes internalization of GluN2B-NMDARs, phosphorylation at tyrosine 1472 (Y1472) by Fyn promotes their membrane insertion (Prybylowski et al., 2005; Chen and Roche, 2007). The abundance of Fyn in both frontal cortex and hippocampus depends on age and sex: (1) Fyn decreases with age as GluN2B switches to GluN2A and (2) males exhibits greater Fyn abundance than females (Sinclair et al., 2016, Figure 5). In schizophrenic patients, there was an increase in Fyn mRNA content (15.7%,) relative to controls (Ohnuma et al., 2003), which corroborates the hypothesis that elevated GluN2B/GluN2A ratio at the synapse is prone to develop schizophrenia.

Fyn Dysregulation in Schizophrenia

Fyn interacts with STEP61 and ErbB4. STEP61, in turn, is under the regulation of brain-derived neurotrophic factor (BDNF).

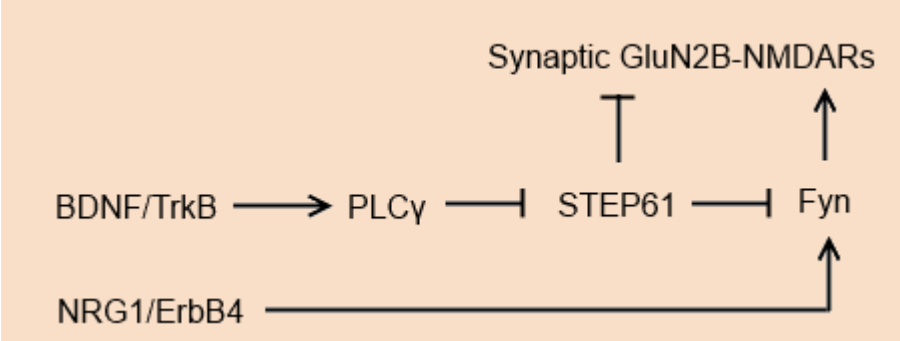

Figure 2. Regulation of synaptic GluN2B-NMDARs. The BDNF/TrkB signaling activates PLCγ to induce STEP61 degradation. Since Fyn is inactivated by STEP61, lower STEP61 level should increase Fyn activity. Hence, BDNF may augment Fyn activity, thereby increasing synaptic GluN2B-NMDARs. STEP61 can also directly promote GluN2B-NMDAR endocytosis by dephosphorylating GluN2B at Y1472. The NRG1/ErbB4 signaling can activate Fyn directly to enhance the surface expression of GluN2B-NMDARs.

STEP61

Striatal-enriched protein tyrosine phosphatase (STEP) has several isoforms (Braithwaite et al., 2006). The longest one, STEP61, can

inactivate Fyn by dephosphorylation at Y420 (Nguyen et al., 2002) or promote GluN2B-NMDAR endocytosis directly by dephosphorylating GluN2B at Y1472 (Trepanier et al., 2012). There were conflicting reports on the level of STEP61 in schizophrenia (Lanz et al., 2015; Carty et al., 2012). According to its functions, reduced STEP61 should aggravate NMDAR hypofunction. This notion is supported by the action of BDNF.

BDNF

Low level of BDNF is associated with Alzheimer's disease (Yasutake et al., 2006) and other neurodegenerative disorders (Howells et al., 2000; Zuccato and Cattaneo, 2007; He et al., 2013; Ventriglia et al., 2013). However, reports on the level of BDNF in schizophrenia are mixed (Gören, 2016). A recent study found that higher serum levels of BDNF are associated with greater severity for negative symptoms (Binford et al., 2018). Furthermore, many drugs that induce schizophrenia-like symptoms **upregulate** BDNF, including ketamine (Autry et al., 2011; Duman et al., 2012), phencyclidine (Takahashi et al., 2006), amphetamine (Shen et al., 2014), cannabinoids (Butovsky et al., 2005; D'Souza et al., 2009), lysergic acid diethylamide (LSD) (Martin et al., 2014) and the phenethylamine hallucinogen DOI (Cui et al., 2018; Jiang et al., 2016). Importantly, BDNF release is required for the behavioral actions of ketamine (Lepack et al., 2014). These results suggest that excess, instead of deficient, BDNF could be prone to develop schizophrenia.

BDNF has been demonstrated to increase synaptic GluN2B-NMDARs through Fyn-mediated phosphorylation on Y1472 (Xu et al., 2006; Hildebrand et al., 2016). Another study showed that the BDNF signaling, which activates phospholipase C gamma (PLCγ) (Paper 4), can induce STEP61 degradation through the ubiquitin-proteasome system (Saavedra et al., 2016). This explains how BDNF may increase synaptic GluN2B-NMDARs (Figure 2).

NRG1/ErbB4

ErbB4 is the tyrosine kinase receptor for Neuregulin 1 (NRG1). In the prefrontal cortex of schizophrenic patients, the NRG1/ErbB4 signaling increases substantially, resulting in NMDAR hypofunction (Hahn et al., 2006). The increase of NRG1 signaling was also observed in treatment-resistant schizophrenia (Mostaid et al., 2017). There are two possible mechanisms: (1) direct activation of Fyn (Bjarnadottir et al., 2007) and (2) mediated by TrkB (Pandya and Pillai, 2014).

The Unique Role of PKA in NMDAR Hypofunction

Protein kinase A (PKA) has the capacity to phosphorylate and inactivate STEP61 (Trepanier et al., 2012). Therefore, higher PKA activity should augment Fyn activity, thereby promoting membrane insertion of GluN2B-NMDARs. This function appears to contradict with the beneficial effects of antipsychotics.

Dopaminergic transmission is dominated by D1 receptors (D1Rs) in the prefrontal cortex, and D2Rs in the striatum (Howes and Kapur, 2009). The D1R signaling stimulates, while the D2R signaling inhibits, the production of cAMP which can activate PKA (Bozzi and Borrelli, 2013). Schizophrenia is characterized by reduced D1R signaling in the prefrontal cortex and hyperactive D2R signaling in the striatum. Hence, in both brain areas, the PKA activity is attenuated. To date, all drugs capable of producing antipsychotic effects are D2R antagonists (Seeman, 2014; Stępnicki et al., 2018) which enhance PKA activity. For instance, the third-generation antipsychotic, aripiprazole, has been demonstrated to increase PKA signaling (Pan et al., 2016).

The mechanism underlying the beneficial effects of PKA activation can be explained by the CABT Hypothesis.

The CABT Hypothesis of NMDAR Hypofunction

How can elevated GluN2B/GluN2A ratio cause NMDAR hypofunction?
The CABT Hypothesis posits that the NMDAR could be blocked by the CABT complex (Figure 3). Both CRMP2 and tubulin have been shown to interact with the GluN2B subunit of NMDARs, not GluN2A (van Rossum et al., 1999; Al-Hallaq et al., 2007; Brittain et al., 2012; Brustovetsky et al., 2014). Therefore, the CABT complex can block only GluN2B-NMDARs, while GluN2A-NMDARs are spared. This explains why NMDAR hypofunction should depend on the GluN2B/GluN2A ratio: the higher the ratio, the more synaptic NMDAR currents could be reduced by CABT occlusion.

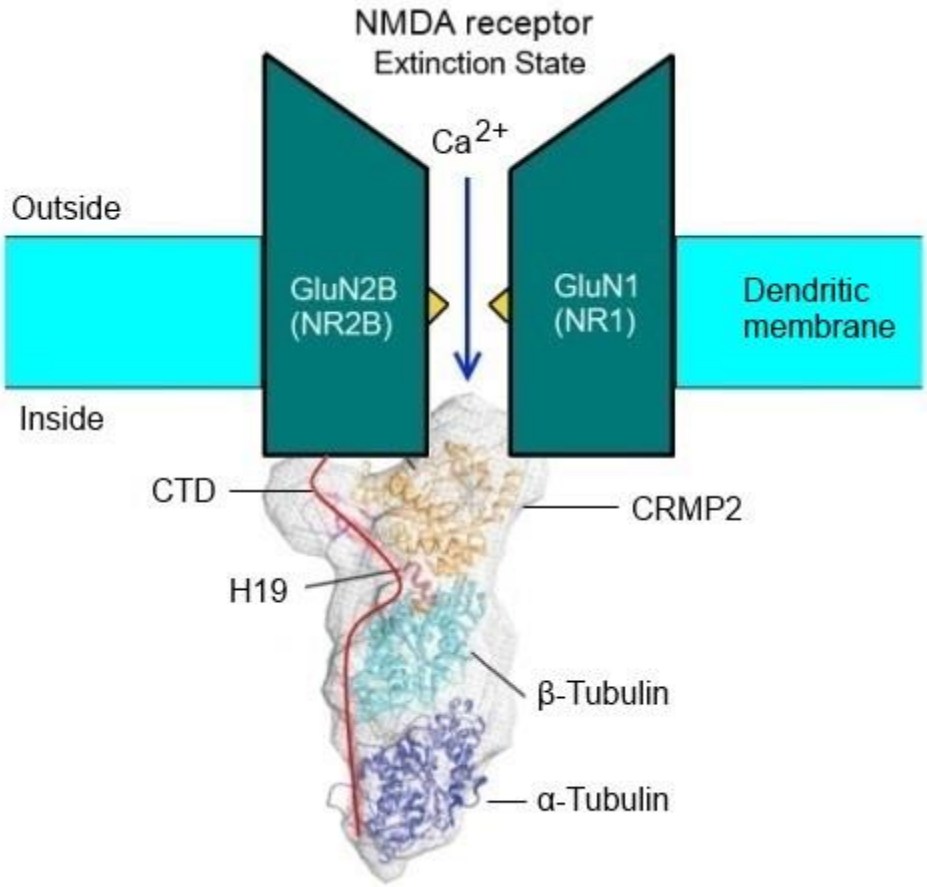

Figure 3. Occlusion of the GluN2B-containing NMDAR by the CABT complex which consist of a CRMP2 monomer, α and β tubulin. This state is called the "extinction state" because it could be the underlying mechanism for memory extinction. PKA can prevent the occlusion by phosphorylating GluN2B at S1166 located in the C-terminal domain (CTD). [The CABT structure is adapted from Niwa et al., 2017]

The CABT Hypothesis was originally proposed to explain "memory extinction" (inhibition of memory retrieval). It is supported by many studies on memory processes (see *Born to Forget, Die to Remember*). Interestingly, the hypothesis can readily explain a well known phenomenon, **infantile amnesia**, i.e., the inability for an adult to recall early childhood memories (Travaglia et al., 2016). The early childhood memories were encoded in the neurons dominated by GluN2B-NMDARs which are subject to CABT occlusion. Consequently, they were severely extinguished and very hard to retrieve. (see Why Can't We Recall Early Childhood Memories? for more detail). In line with this hypothesis, schizophrenic patients are harder than healthy people in

retrieving memories (Holt et al., 2009; Holt et al., 2012), possibly because they have higher GluN2B/GluN2A ratio.

The NMDAR hypofunction should also depend on the binding between CABT and GluN2B, in which PKA plays the most critical role. Phosphorylation of GluN2B at S1166 by PKA prevents CABT from occluding GluN2B-NMDARs, thereby increasing NMDAR currents (see Paper 24 for detail). As discussed in the next section, GSK-3 also participates in the regulation of CABT-GluN2B binding.

Arc Could be the Long-Sought Target of GSK-3

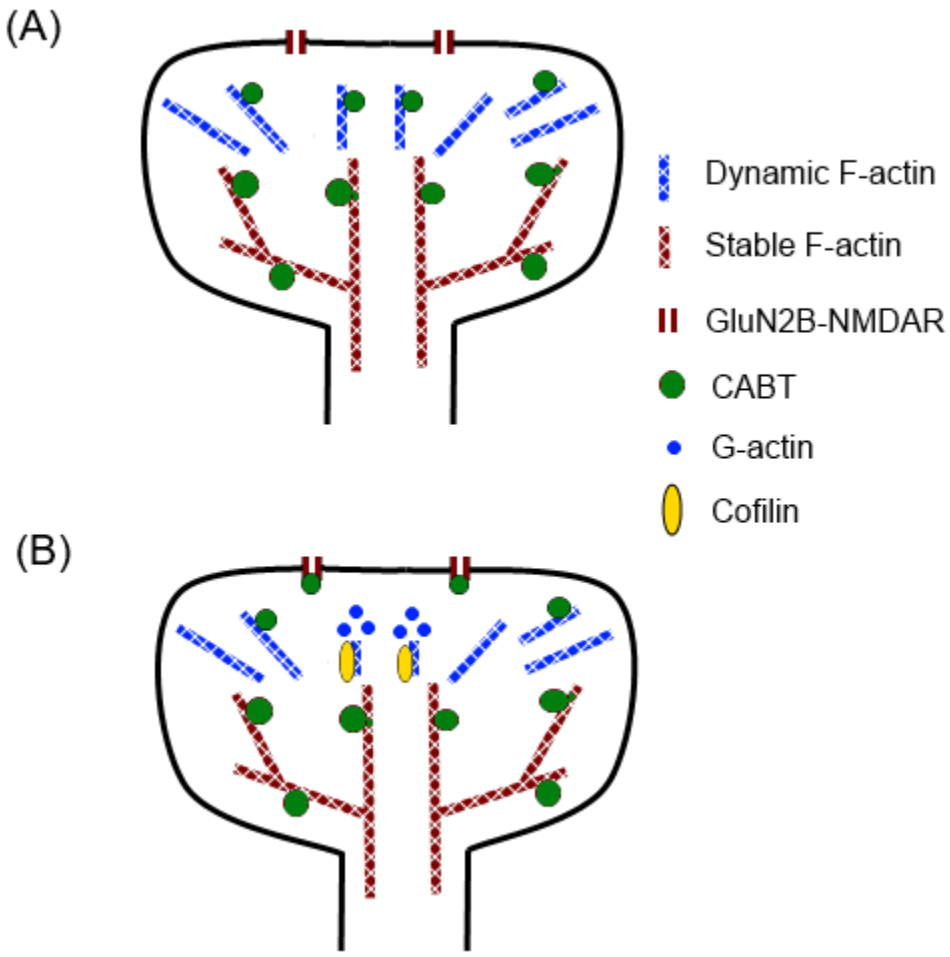

Figure 4. A model for the regulation of CABT-GluN2B binding by actin depolymerization.
(A) The CABT complex binds to both dynamic and stable F-actin.
(B) Depolymerization of the dynamic F-actin by cofilin

causes CABT to bind and block GluN2B-containing NMDARs, resulting in NMDAR hypofunction.

In the past few years, evidence was rapidly accumulating that the activity-regulated cytoskeleton-associated protein (Arc) might be one of the primary players in schizophrenia (Managò and Papaleo, 2017). It was found that a few genes implicated in schizophrenia are related to Arc (Fromer et al., 2014; Purcell et al., 2014). Furthermore, genetic disruption of Arc leads to characteristics of schizophrenia: hyperactive and hypoactive dopamine signaling in the striatum and prefrontal cortex, respectively. Application of a D1R agonist to the prefrontal cortex or a D2R antagonist in the striatum rescues Arc-dependent abnormalities (Managò et al., 2016).

The dendritic spine is enriched with actin. Arc plays a critical role in the formation of filamentous actin (F-actin) by counteracting cofilin which may depolymerize F-actin into globular actin (G-actin) monomers (Bramham et al., 2008). F-actin generally undergoes turnover by continuous "treadmilling" which involves the polymerization of G-actin at one end of the filament and depolymerization of F-actin at the opposite end. Based on the turnover rate, two distinct pools of F-actin have been observed: dynamic and stable (Honkura et al., 2008). The dynamic pool has rapid turnover, located near the spine tip whereas the stable pool is closer to the base of the spine head (Figure 4).

The CABT complex consists of a CRMP2 monomer and a tubulin heterodimer. Colocalization of the CABT complex with F-actin has been observed in neurites (Tan et al., 2015; Yang et al., 2015). Therefore, in the spine, CABT may bind either F-actin or GluN2B. Binding of CABT to F-actin would not block NMDAR currents. However, if F-actin is depolymerized, CABT would be forced to bind GluN2B, which may reduce NMDAR currents. Since Arc plays a critical role in stabilizing F-actin, this explains why Arc deficiency may cause NMDAR hypofunction. In support of this mechanism, actin polymerization has been found to decrease in the anterior cingulate cortex of elderly patients with schizophrenia (Bhambhvani et al., 2017). As mentioned above, Arc-dependent abnormalities can be rescued by D1R agonist in the prefrontal cortex or a D2R antagonist in the striatum. In both cases, the PKA activity increases, which may prevent the CABT-GluN2B binding.

GSK-3 is a convergent target of most antipsychotics (Beaulieu, 2012). It has a plethora of substrates. Which one is critical for the regulation of NMDAR functions remains elusive. Remarkably, a recent study demonstrates that GSK-3 promotes Arc degradation (Gozdz et al.,

2017). This finding suggests that Arc could be the long-sought target of GSK-3 in the pathogenesis of schizophrenia. Hyperactive GSK-3 could cause Arc deficiency, promoting CABT-GluN2B binding, thereby resulting in NMDAR hypofunction. Antipsychotics may augment NMDAR currents by inhibiting GSK-3 to increase the Arc level.

How Shank3 Deficiency Causes NMDAR Hypofunction

Shank3 is a scaffold protein that links NMDARs to other components in the postsynaptic density (Gao et al., 2013). It is implicated in schizophrenia and autism (Gauthier et al., 2010; Uchino and Waga, 2013; Zhou et al., 2016). Shank3 deficiency has been shown to reduce synaptic currents mediated by NMDARs (Kouser et al., 2013; Jaramillo et al., 2016), but its underlying mechanism is unclear. Several lines of evidence suggest that actin is involved (Duffney et al., 2013). It was proposed that Shank3 deficiency may promote F-actin depolymerization by enhancing cofilin activity (Duffney et al., 2015). Further details are described in another article.

Akt/GSK-3 vs. Akt/mTOR pathway

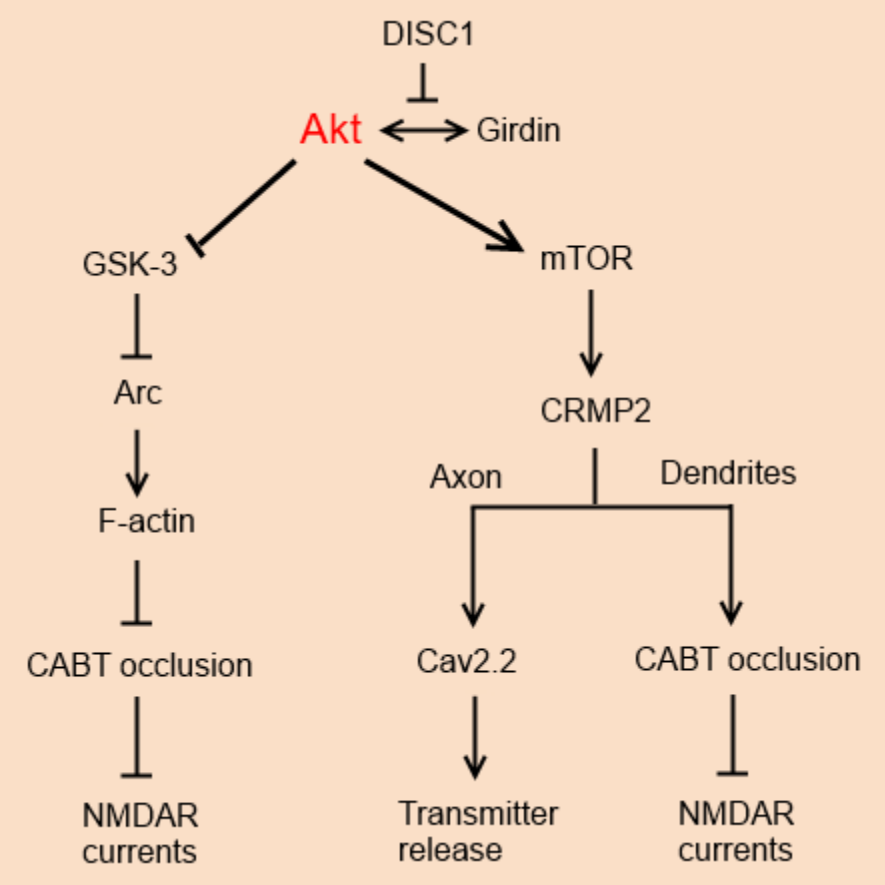

Figure 5. Akt signaling pathways. DISC1 has been shown to suppress Akt activity by inhibiting Girdin-Akt interaction. Activation of Akt by various upstream signals (not shown) may inhibit GSK-3 or activate mTOR. The Akt/GSK-3 pathway could increase NMDAR currents by preserving Arc to facilitate CABT/F-actin binging, thereby reducing CABT occlusion on GluN2B-NMDARs. The Akt/mTOR pathway can stimulate CRMP2 translation. In dendritic spines, elevated CRMP2 protein level promotes NMDAR hypofunction by forming complexes with tubulin to block GluN2B-NMDARs. In the axon terminal, CRMP2 may promote membrane insertion of Cav2.2 to enhance neurotransmitter release.

Akt is widely accepted as a key player in the development of schizophrenia (Kim et al., 2009). The first-generation antipsychotics are D2R antagonists which augment Akt activity while the second-generation (atypical) antipsychotics also act on 5-HT2A receptors which may not influence Akt activity (Beaulieu, 2012). According to CABT Hypothesis, Akt is a double-edged sword. Its downstream

effectors, GSK-3 and mechanistic target of rapamycin (mTOR) may exert opposite effects on NMDAR functions (Figure 5).

GSK-3 has two isoforms: GSK-3α and GSK-3β. They are constitutively active, but can be inactivated through the phosphorylation of a single residue: serine 21 for GSK-3α and serine 9 for GSK-3β. Akt may phosphorylate GSK-3 and inhibit its activity. Most antipsychotics lead to the inhibition of GSK-3 activity (Beaulieu, 2012). As explained above, GSK-3 inhibition may increase NMDAR currents by preserving Arc to stabilize F-actin for the binding with CABT.

mTOR is a protein kinase that catalyzes protein phosphorylation. Upon activation, it can phosphorylate two major targets, p70 ribosome S6 kinase (p70S6K) and eukaryotic initiation factor 4E-binding protein 1 (4EBP1), to initiate protein synthesis from mRNA. Remarkably, the translation of CRMP2 protein from its mRNA is regulated by mTOR (Morita and Sobue, 2009; Mita et al., 2016; Na et al., 2017; Ben Hamida et al., 2018). Therefore, the Akt/mTOR pathway can increase CRMP2 protein level in the dendritic spine, which promotes NMDAR hypofunction by forming complexes with tubulin to block GluN2B-NMDARs. In support of this mechanism, ketamine has been shown to accelerate fear extinction via mTOR signaling in the medial prefrontal cortex (Girgenti et al., 2017).

The "disrupted in schizophrenia 1" (DISC1), as the name implies, is strongly implicated in schizophrenia. It may regulate Akt activity through Girdin (= KIAA1212). The interaction between Girdin and Akt strengthens the activation (phosphorylation) of Akt, but their interaction can be inhibited by DISC1 (Kim et al., 2009). In addition, DISC1 can directly inhibit GSK-3 (Mao et al., 2009). Hence, DISC1 always increases NMDAR currents although activation of Akt may lead to opposite effects on NMDAR functions.

CRMP2 is also enriched in axon terminals where it plays a crucial role in axon elongation (Goshima et al., 1995; Fukata et al., 2002). In addition, CRMP2 may bind the N-type calcium channel Cav2.2, promoting its membrane insertion (Brittain et al., 2009). The increased Ca^{2+} influx in the axon terminal may enhance the release of neurotransmitters, such as glutamate (Lu et al., 2018) and dopamine (Bergquist et al., 1998). Reduced glutamate release could also lead to NMDAR hypofunction.

Discussion

BDNF plays critical roles in many aspects of brain functions. Insufficient BDNF could cause neurodegenerative disorders (Paper 4). However, most drugs capable of inducing schizophrenia-like symptoms **increase** BDNF, suggesting that excess BDNF could be prone to develop schizophrenia. This notion is supported by the finding that BDNF release is required for the behavioral actions of ketamine (Lepack et al., 2014).

Theories on the pathogenesis of schizophrenia were dominated by Dopamine Hypothesis for several decades, but recent studies are in favor of the NMDAR Hypofunction Hypothesis. It has been shown that the Dopamine Hypothesis is actually a consequence of NMDAR Hypofunction Hypothesis (Figure 1). The mechanism of NMDAR hypofunction remains unclear. In Paper 19, the CABT hypothesis was proposed to explain the mechanism of memory extinction (inhibition of memory retrieval). It posits that NMDARs could have an "extinction state" resulting from the occlusion by the CABT complex which is formed by a CRMP2 monomer and a tubulin heterodimer (Figure 3). Posttraumatic stress disorder is characterized by the inability to forget or extinguish traumatic events. It is associated with **low level** of BDNF (Paper 20). Interestingly, memory extinction is also impaired in schizophrenia, but in the opposite direction: schizophrenic patients are harder to retreive memories (Holt et al., 2009; Holt et al., 2012). These results indicate that the NMDAR hypofunction in schizophrenia could also result from the occlusion of NMDARs by the CABT complex.

Both CRMP2 and tubulin have been demonstrated to bind GluN2B, not GluN2A. Therefore, the CABT complex can block only GluN2B-NMDARs, without affecting GluN2A-NMDARs. Consequently, the NMDAR hypofunction should depend on the GluN2B/GluN2A ratio, as well as the binding between CABT and GluN2B. Based on the CABT hypothesis, BDNF may aggravate NMDAR hypofunction through two pathways: (1) BDNF/PLCγ/STEP61/Fyn (Figure 2), and (2) BDNF/PI3K/Akt/mTOR. The first pathway activates Fyn which promotes the membrane insertion of GluN2B-NMDARs, thereby increasing the GluN2B/GluN2A ratio. The second pathway activates mTOR which stimulates the synthesis of CRMP2 protein from its mRNA. Higher CRMP2 level in the spine could form more CABT complexes to block GluN2B-NMDARs.

PKA is the most critical factor in the regulation of CABT-GluN2B binding. When GluN2B is phosphorylated at S1166 by PKA, CABT cannot bind and block GluN2B-NMDARs. Its structural basis has been discussed in Paper 24. Another important factor is actin polymerization. CABT may bind either F-actin or GluN2B-NMDARs.

If F-actin is depolymerized, CABT would be forced to bind GluN2B-NMDARs, thereby promoting NMDAR hypofunction. GSK-3 may exacerbate NMDAR hypofunction by inducing Arc degradation since Arc plays a critical role in stabilizing F-actin.

The signaling induced by most antipsychotics lead to GSK-3 inhibition (Beaulieu, 2012). Lithium is a well-documented GSK-3 inhibitor (Stambolic et al., 1996). Surprisingly, lithium exerts little beneficial effects on schizophrenia (Leucht et al., 2015). This could arise from the upregulation of BDNF by lithium (Fukumoto et al., 2001; Dwivedi and Zhang, 2015). In line with this mechanism, lithium has been commonly prescribed for the treatment of bipolar disorder, which is associated with **decreased** BDNF level (Kapczinski et al., 2008).

CRMP2 is encoded by the *DPYSL2* gene which is implicated in schizophrenia (Liu et al., 2014; Pham et al., 2016). It has three subtypes: A, B and C. The CRMP2B protein (encoded by DPYSL2B) contains 572 amino acids (aa) while CRMP2A comprises 677 aa. In the brain, CRMP2B is ~20 times more abundant than CRMP2A (Balastik et al., 2015). Perhaps for this reason, previous studies focused on CRMP2B. However, CRMP2A, being a larger protein, could be more effective in occluding GluN2B-NMDAR2 than CRMP2B. Strikingly, the expression of DPYSL2A (but not DPYSL2B) is correlated with sex: higher expression in males (Liu et al., 2014), which may contribute to the higher incidence of schizophrenia in males.

In the 5′-untranslated region of DPYSL2, there is a CT di-nucleotide repeat (DNR) which responds to mTOR signaling. In Caucasians, this DNR most often comprises 11 CT repeats (11DNR). The polymorphic 13 CT repeats (13DNR) increases the risk for schizophrenia (Pham et al., 2016). It has been demonstrated that 13DNR is associated with reduced CRMP2B level (Liu et al., 2014). This result is not predicted by CABT Hypothesis as reduced CRMP2 level in spines is supposed to attenuate occlusion of GluN2B-NMDARs by the CABT complex. However, in axon terminals, the reduction of CRMP2B may attenuate Cav2.2-induced glutamate release (Figure 5), leading to NMDAR hypofunction in the postsynaptic neuron. The effects of DNR polymorphism on schizophrenia could result from this mechanism.

Several lines of evidence suggest that, in most cases, schizophrenia could result from elevated CRMP2 in dendrites, rather than reduced level of CRMP2 in the axon.

1. Vitamin D is an mTOR inhibitor (Lisse and Hewison, 2011). Lower vitamin D levels are found in schizophrenic patients (Berg et al., 2018; Chiang et al., 2016). Prenatal vitamin D supplementation decreased the risk for schizophrenia (Freedman et al., 2018).

2. Ketamine augments mTOR signaling (Harraz et al., 2016).

3. The defects induced by DISC1 suppression can be rescued by pharmacological inhibition of mTOR (Kim et al., 2009; Zhou et al., 2013).

Notably, translation of CRMP2A is not affected by DNR polymorphism (Pham et al., 2016). The expression of CRMP2A is higher in males than females (Liu et al., 2014), consistent with higher incidence of schizophrenia in males. Furthermore, CRMP2A is a larger protein than CRMP2B. It is present in both dendrites and distal axons (Balastik et al., 2015). The dendritic CRMP2A could play an important role in NMDAR hypofunction by occluding GluN2B-NMDARs.