From understanding synaptic plasticity to the development of cognitive enhancers

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Abstract
Accumulating evidence reveals that synaptic dysfunction precedes neuronal loss in neurodegenerative diseases such as Alzheimer’s disease. Intriguingly, synaptic abnormality is also implicated in a myriad of psychiatric disorders including depression. In particular, alterations in spine density and morphology have been associated with aberrant synaptic activity in these diseased brains. Understanding the molecular mechanisms underlying the regulation of spine morphogenesis, synaptic function and plasticity under physiological and pathological conditions will therefore provide critical insights for the development of potential therapeutic agents against these diseases. Here we summarize existing knowledge on some of the molecular players in synaptic plasticity, and highlight how these findings from basic neuroscientific research aid in the identification of novel drug leads for the development of therapeutics.

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Introduction
Since the first depiction of neurons by Ramon y Cajal more than a century ago, remarkable progress has been made to unveil the mystery behind the physiology, functioning and communication by these unique cells. With the commencement of the molecular and genetic era, knowledge on the molecular pathways implicated in the control of neuronal survival, synaptic transmission and synaptic plasticity have exploded. As much as these findings reveal how the neuronal circuitry mediates daily physiological function of the nervous system, they also provide essential information for deciphering the molecular pathophysiology of various neurological disorders. For example, aberrant synaptic transmission has been implicated in psychiatric disorders such as schizophrenia and depression, whereby the level of neurotransmitters is abnormally elevated or reduced, affecting neurotransmission. On the other hand, studies aimed at elucidating the pathophysiological mechanisms of neurodegenerative diseases have focused on identifying the signalling pathways that mediate the selective degeneration of the susceptible neuronal populations in these diseases. Interestingly, mounting evidence indicates that loss of synapses precedes actual neuronal death in Alzheimer’s disease (AD) (Selkoe, 2002). In addition, advances in unravelling the molecular mechanisms of depression point unexpectedly to deregulation in synaptic plasticity (Krishnan & Nestler, 2008; Pittenger & Duman, 2008). It therefore appears that dysfunction in synaptic transmission and plasticity may present a common pathogenic mechanism across a broad spectrum of neurological disorders. This realization underscores the significance of in-depth investigations into the molecular control of synapse function and plasticity, as these findings are likely to generate critical new insights into the future development of therapeutics that may be applicable to multiple disorders harbouring synaptic failures. In this brief review, we summarize the current understanding of the molecular mechanisms underlying the control of synaptic function and plasticity in AD and depression, as examples of neurodegenerative disease and psychiatric disorder. How this knowledge may be utilized to identify novel drug targets will also be discussed.
Aberrant synaptic function and plasticity as a common pathophysiological mechanism in AD and depression

Aberrant synaptic function

AD is the leading cause of dementia worldwide and accounts for more than 50% of dementia cases. Post-mortem brains of AD patients are characterized by the presence of extracellular aggregates composed predominantly of β-amyloid (also known as Aβ) and intracellular neurofibrillary tangles of hyperphosphorylated tau. Aβ generation has been postulated as the main culprit in the aetiopathology of AD, as supported by its abundant presence in senile plaques and the observation that essentially all missense mutations identified in familial cases of AD result in elevated production of Aβ (Hardy & Selkoe, 2002). Aβ is generated from sequential cleavage of a transmembrane protein called amyloid precursor protein (APP) by β-secretase and γ-secretase (Wasling et al. 2009). Since AD is a neurodegenerative disease in nature, earlier efforts have been directed at understanding the molecular mechanisms by which Aβ generation is regulated, and how Aβ deposits lead to death of the neurons. Nonetheless, subsequent evidence indicates that decrease in synapse density precedes actual loss of neurons in AD brains. More importantly, synaptic loss, rather than neuron loss, serves as a more accurate correlate with cognitive decline in AD patients (Selkoe, 2002). An increasing number of studies have therefore focused on elucidating the effect of Aβ on synaptic functions.

Several lines of evidence indicate that Aβ can directly impair synaptic transmission in AD. Glutamate is the major excitatory neurotransmitter in the brain. There are two subtypes of ionotropic glutamate receptors, namely the AMPA receptors (AMPArs) and the NMDA receptors (NMDARs). While AMPARs are directly activated by ligand binding and mediate fast excitatory transmission at the synapse, NMDAR activation requires concurrent ligand binding and depolarization of the post-synaptic neuron. This unique property of NMDARs renders them particularly important in synaptic plasticity. NMDARs function as ‘coincidence detectors’, allowing the selective, long-term strengthening of synaptic transmission following high-frequency stimulation of the synapse in the cellular paradigm of long-term potentiation (LTP). Indeed, activation of NMDARs was demonstrated to be essential for the generation of synaptic plasticity in the brain (Lau & Zukin, 2007). Interestingly, Aβ has been observed to selectively affect glutamatergic synapses (Wasling et al. 2009). Transgenic mice harbouring various mutations in APP, which lead to elevated Aβ generation, exhibit impaired synaptic transmission and LTP (Parsons et al. 2007; Selkoe, 2002; Wasling et al. 2009). Interestingly, loss of post-synaptic marker PSD-95 around Aβ plaques in an APP transgenic mouse is paralleled by reduction in pre-synaptic boutons, suggesting that synapse loss involves both pre-synaptic and post-synaptic elements (Spires et al. 2005). Aβ treatment in vitro and in vivo also decreases surface glutamatergic receptor-mediated signals and LTP (Hsieh et al. 2006; Selkoe, 2002; Wasling et al. 2009), and reduces surface expression of NMDAR subunit NR1 by promoting its internalization (Kurup et al. 2010; Snyder et al. 2005). This is accompanied by diminished NMDAR current and the downstream activation of transcription factor CREB (Kurup et al. 2010; Snyder et al. 2005). In addition, AMPAR removal was found to underlie Aβ-stimulated synaptic depression and spine loss (Hsieh et al. 2006). Taken together, these observations indicate that Aβ can directly impair synaptic functions and plasticity in AD brains by interfering with glutamatergic synapses.

Another neurological disorder characterized by aberrant synaptic function is depression. Also known as major depressive disorder, depression is a psychiatric disorder characterized by low mood, irritability, anhedonia, difficulty in concentrating and cognitive impairment. While the cause is essentially unknown, earlier studies aimed at elucidating the mechanisms of action of antidepressants suggest that reduced transmission of two monoamine neurotransmitters in the brain, namely 5-HT (serotonin) and noradrenaline, plays a pathophysiological role in depression (Krishnan & Nestler, 2008; Pittenger & Duman, 2008). Interestingly, accumulating evidence suggests that impaired synaptic plasticity may also play a role in depression. Indeed, depressed patients exhibit difficulty in declarative memory (Zakzanis et al. 1998). Stress, which is a known precipitating and aggravating factor of depression, has been demonstrated to disrupt hippocampal LTP in experimental animals, in addition to inducing atrophy of hippocampus, a situation also observed in depressed patients (Calabrese et al. 2009; Chen et al. 2010; Pittenger & Duman, 2008). Expression of brain-derived neurotrophic factor (BDNF), a neurotrophic factor that is critical for synaptic plasticity, was reduced in the hippocampus of post-mortem brains of depressed patients (Karege et al. 2005). In addition, antidepressant treatment enhances the expression of BDNF and transcription factor CREB, which have been demonstrated as pivotal players in long-term synaptic plasticity.
Spine morphology anomaly

The majority of the excitatory synapses are located on tiny protrusions on dendrites known as spines. Spines are highly dynamic structures, with their size, shape and density along dendrites under constant and at times, rapid, regulation. While the more elongated protrusions known as filopodia are regarded as immature spines and are highly plastic; stubby, mushroom-shaped spines are generally mature spines that are more stable in nature (Tada & Sheng, 2006). Interestingly, spine morphogenesis is regulated by synaptic activity, and has been postulated as the structural basis of synaptic plasticity. LTP, for example, is associated with an enlargement of spine head and insertion of AMPARs at synaptic sites; while long-term depression (LTD) involves shrinkage of spines (Dillon & Goda, 2005; Lau & Zukin, 2007; Tada & Sheng, 2006; Zhou et al. 2004). Changes in spine morphology require the coordinated regulation of actin cytoskeleton and also gene transcription (Ethell & Pasquale, 2005). Given the essential role of spine morphogenesis in synaptic plasticity, understanding how spine morphology is altered in various neurological diseases will provide essential background knowledge on how synaptic dysfunction may be reversed.

In addition to directly impairing synaptic transmission and plasticity by interfering with glutamatergic synapses, Aβ has also been demonstrated to affect spine morphogenesis. Aβ treatment has been observed to reduce dendritic spine density in cultured neurons and also in transgenic animal models of AD (Knobloch & Mansuy, 2007; Shankar et al. 2007; Spires et al. 2005). In particular, a recent study demonstrated that Aβ produced from axons or dendrites lowers spine number and plasticity on nearby dendrites (Wei et al. 2010). These observations suggest that loss of dendritic spines may also contribute to the cognitive deficits in AD patients.

Changes in spine morphology in depression are not as well documented but evidence in support of this possibility is beginning to emerge. Chronic stress was observed to reduce dendritic complexity (Bloss et al. 2010; Hains et al. 2009; Liston et al. 2006), in addition to decreasing spine density in rats (Chen et al. 2008b, 2010; Hains et al. 2009; Radley et al. 2006; Silva-Gomez et al. 2003). In addition, a recent study demonstrated that post-mortem brains of human patients with severe stress and longitudinal depression exhibit reduced dendritic spine densities (Soetanto et al. 2010). In agreement with these findings, treatment with antidepressants fluoxetine or imipramine enhance spine density in rats (Ampuero et al. 2010; Chen et al. 2008a; Hajsan et al. 2005), implicating structural changes in dendritic spines and synaptic abnormality in depressed patients.

Molecular players in the regulation of synaptic functions and spine morphogenesis

A plethora of signalling pathways has been implicated in the control of synaptic functions. Nonetheless, recent studies have highlighted several molecular players that show promise in allowing identification of novel targets for developing drugs that can reverse synaptic abnormality.

Glutamate receptors

Being the receptors for the major excitatory synapses in the brain, it is no surprise that glutamate receptors are pivotal for the control of synaptic strength. The type and number of glutamate receptors present at a synapse are under tight dynamic regulation and serve as one of the most direct determining factors of synaptic strength. Rapid changes in the number of glutamate receptors are mediated by insertion or removal of surface receptors at the post-synaptic densities. Lateral movement of both AMPA and NMDA receptors also contributes to the rapid changes in glutamatergic transmission at the synapse (Hanley, 2008; Lau & Zukin, 2007). Furthermore, AMPA and NMDA receptors play distinct roles in the induction of LTP. NMDAR activation during the concurrent presence of synaptic glutamate and post-synaptic depolarization results in calcium influx through the NMDAR and activation of secondary signalling messengers such as Ca2+ / calmodulin-dependent kinase 2 (CaMKII). The subsequent AMPAR insertion mediates the increase in synaptic strength during LTP induction (Lau & Zukin, 2007; Monti & Contestabile, 2009). The signalling cascade initiated downstream of NMDAR activation also triggers gene transcription, which has been demonstrated to be critical for the late phase of LTP (Kelleher et al. 2004). Aside from being indispensible for glutamatergic transmission and synaptic plasticity, recent evidence suggests that AMPARs may also directly regulate spine morphogenesis. The extracellular N-terminal domain of the AMPAR subunit GluR2 was found to enhance spine growth (Passafaro et al. 2003;
Saglietti et al. (2007). Collectively these observations underscore the essential role of glutamate receptors in the control of synaptic function and plasticity. Interestingly, as much as glutamate transmission is required for normal function of the neural circuitry, excessive activation of glutamate receptors during pathological condition can also impair synaptic function and lead to excitotoxic neuronal loss. Energy failure or impairment of glutamate transporters in AD brains may contribute to an abnormally high level of extracellular glutamate, leading to excitotoxicity (Lipton, 2006; Parsons et al. 2007). In support of a role of excitotoxicity in AD, memantine, an uncompetitive NMDAR antagonist approved by the FDA for the treatment of AD, was found to reduce neuronal loss and also LTP impairment induced by Aβ treatment or in animal models of AD (Lipton, 2006; Parsons et al. 2007; Rammes et al. 2008). The mechanism by which an NMDAR antagonist may reverse LTP impairment has not been completely elucidated, but it appears to involve reduction of tonic activation of glutamatergic synapses (Lipton, 2006; Parsons et al. 2007; Rammes et al. 2008). These findings reveal that although NMDARs may be a very attractive target for development of therapeutics, identifying compounds that inhibit pathological but not physiological glutamatergic transmission will be essential for ensuring the feasibility and applicability of these potential drugs.

**BDNF/TrkB signalling**

BDNF is a member of the neurotrophin family that has been increasingly implicated in the regulation of synaptic function and plasticity. Action of BDNF is mediated predominantly by receptor tyrosine kinase TrkB, although it also binds with low affinity to p75. BDNF is synthesized as proBDNF, which has long been regarded simply as the unprocessed form of mature BDNF. Nonetheless, recent evidence reveals that proBDNF is also secreted, and exhibits high-affinity binding to p75 (Lu et al. 2005). While the neurotrophins were initially identified based on their ability to maintain neuronal survival, BDNF was later identified as being particularly critical for synaptic plasticity. Mice lacking BDNF exhibit impaired LTP induction (Korte et al. 1995; Patterson et al. 1996). In addition, BDNF was found to be secreted at the synapse in an activity-dependent manner. This local elevation in BDNF results in TrkB activation at the synapses, and the subsequent initiation of downstream signalling cascade modulates synaptic proteins to regulate the efficiency of synaptic transmission. These modulations were found to be critical for the early phase of LTP (Waterhouse & Xu, 2009). TrkB activation at the synapse also enhances local protein synthesis, an action that is required for the late phase of LTP (Bramham, 2008). Indeed, BDNF stimulation and depolarization increases trafficking of TrkB and BDNF mRNA to the dendrite (Righi et al. 2000; Tongiorgi et al. 1997), further supporting an involvement of local protein synthesis in synaptic plasticity. On the other hand, proBDNF was found to facilitate LTD induction (Woo et al. 2005). Interestingly, cleavage of proBDNF to mature BDNF is elevated by high-frequency stimulation, one of the stimulation paradigms used to induce LTD in hippocampal slice preparation (Nagappan et al. 2009). These observations indicate that while BDNF signalling is crucial for synaptic function and plasticity, its role is complex and can be controlled at multiple levels.

Aside from being critical for LTP induction, BDNF has also been demonstrated to directly regulate spine morphogenesis and has also been demonstrated to increase spine density (Amaral & Pozzo-Miller, 2007; Ji et al. 2005). Induction of spine head enlargement by pairing of post-synaptic spike with glutamate uncaging was found to require BDNF and local protein synthesis (Tanaka et al. 2008). Furthermore, when dendritic targeting of BDNF mRNA is abolished by expression of a truncated form of the long 3′-UTR BDNF mRNA, impairment in spine head enlargement and spine pruning are observed (An et al. 2008). These findings demonstrated that BDNF also plays a role in spine morphogenesis, in part through regulation of local protein synthesis (Fig. 1).

Extensive studies have demonstrated suppression of BDNF signalling in AD and depression. Both expression of BDNF and TrkB are reduced in AD brains (Schindowski et al. 2008). Interestingly, it was recently demonstrated that BDNF deprivation enhances Aβ generation in hippocampal neurons (Matrone et al. 2008). In agreement with this observation, BDNF was found to reduce Aβ production through activation of Sorting protein-related receptor with A-type repeats (SORLA), whose expression is reduced in sporadic AD (Rohe et al. 2009). These observations reveal that BDNF signalling may be important for reducing Aβ generation in AD brains. On the other hand, while an earlier observation of reduced BDNF level in the hippocampus of depressed patients has triggered considerable interest in the hypothesis that BDNF deficiency may underlie the pathophysiology of depression, recent data are more controversial. For example, reduction of BDNF in the hippocampus is accompanied by elevated BDNF level in the nucleus accumbens (Krishnan & Nestler, 2008). In addition, while a reduction in
BDNF level fails to induce depression, BDNF is required for the efficacy of antidepressants (Calabrese et al. 2009; Krishnan & Nestler, 2008). Taken together these observations reveal that while BDNF is probably involved in the pathophysiology of depression, its action is likely region-specific and additional studies will be required to delineate its precise involvement.

**Cyclin-dependent kinase 5 (Cdk5)**

Cdk5 is a predominantly neural-specific serine/threonine kinase that has recently been implicated in the regulation of synaptic function and plasticity (Cheung et al. 2006; Lai & Ip, 2009). Cdk5 is activated upon binding to its activator p35 or p39. Earlier studies demonstrated that Cdk5 and its activators are expressed at the synapse (Cheung et al. 2006). Evidence in support of a role of Cdk5 in the regulation of synaptic transmission came from the observation that Cdk5 was found to directly phosphorylate NMDAR subunit NR2A, and inhibition of this phosphorylation reduces NMDA-evoked current (Li et al. 2001). In addition, a recent study revealed that inhibition of Cdk5 activity reduces activity-dependent internalization of NMDARs by modulating phosphorylation of the NMDAR subunit NR2B by Src (Zhang et al. 2008). Interestingly, Cdk5 was found to mediate degradation of NR2B by calpain. This is accompanied by improved spatial learning in Cdk5 conditional knockout mice (Hawasli et al. 2007). These observations implicate Cdk5 in the regulation of glutamate transmission and synaptic plasticity. Furthermore, Cdk5 has also been demonstrated to regulate spine morphogenesis. Cdk5 was found to be required for ephrinA1-induced spine retraction through regulation of the downstream activation of RhoA (Fu et al. 2007). In addition, Cdk5 phosphorylates WAVE1 to inhibit actin polymerization. This is associated with reduction of stubby-shaped spines (Kim et al. 2006). These observations reveal that Cdk5 is pivotal for the regulation of spine morphogenesis.

Cdk5 has long been implicated in the pathophysiology of AD. In particular, cleavage of p35 into a p25 fragment, which results in prolonged activation of Cdk5, is associated with neuronal loss in various models of neurodegenerative diseases (Cheung et al. 2006). Indeed, Cdk5 was initially identified as a tau kinase (Kobayashi et al. 1993). In addition, neuronal loss and impairment in spatial learning are evident in a mouse model with prolonged expression of p25 (Fischer et al. 2005). Interestingly, expression of β-secretase BACE1 is also elevated in this strain of mouse, leading to elevated production of Aβ (Wen et al. 2008). These studies collectively indicate that...
aberrant activation of Cdk5 may contribute to the pathophysiology of AD.

A role of Cdk5 in depression is not as solidly demonstrated. Nonetheless, Cdk5 has been observed to regulate dopamine signalling, the dysfunction of which has been associated with the pathophysiology of depression (Rakofsky et al. 2009). Cdk5 was demonstrated to phosphorylate DARPP-32, an important player in dopamine signalling. Cdk5-mediated phosphorylation of DARPP-32 reduces dopamine-induced activation of PKA, thereby attenuating dopaminergic signalling (Benavides & Bibb, 2004). These observations suggest that Cdk5 may, through its modulation of dopaminergic signalling, contribute to monoamine imbalance in depressed patients. Further studies will be required to address the precise role of Cdk5 in depression.

Identification of novel drug leads that target regulators of synaptic plasticity

Basic research focused on understanding the pathophysiology of various diseases is crucial for the development of therapeutic interventions. Explicating the signalling pathways that are affected in the disorder will enable the identification of proteins that may be targeted to ameliorate symptoms or delay disease progression. Through the uncovering of novel molecular players, drug leads that directly target these molecules can then be developed and tested as potential therapeutics against the disease (Fig. 2). This approach has served as one of the most important strategies for effective design and development of drugs and treatment against various disorders. Indeed, advances in understanding the molecular mechanisms implicated in the pathophysiology of neurological disorders such as AD and depression have led to the development of the existing treatments for these diseases. For example, the observed reduction in cholinergic transmission in post-mortem AD brains prompted the development of AChE inhibitors as therapeutic agents for AD (Monti & Contestabile, 2009). However, recent evidence has revealed that inhibition of nicotinic acetylcholine receptors reduces Aβ production and Aβ-induced spine loss (Wei et al. 2010), raising the possibility that activation of nicotinic acetylcholine receptors by increasing acetylcholine level via AChE inhibition may be detrimental. On the other hand, the induction of excitotoxic death following Aβ treatment and evidence of excitotoxicity in AD brains lead to the exploration of NMDAR antagonists as potential neuroprotective agents against neuronal loss (Lipton, 2006). Many clinical trials have been performed with various NMDAR antagonists but since physiological level of glutamate transmission is pivotal for the normal function of the brain, many of the antagonists tested resulted in major side-effects and the studies were discontinued. Memantine, currently the only NMDAR antagonist approved for the treatment of AD, is unique as a non-competitive, relatively low-affinity, open-channel antagonist that exhibits strong voltage-dependence and fast off-rate (Lipton, 2006; Monti & Contestabile, 2009; Rammes et al. 2008). This special property of memantine allows it to preferentially bind to NMDARs that are open for a prolonged period, without interfering with the normal physiological function of the receptor (Lipton, 2006; Monti & Contestabile, 2009; Rammes et al. 2008). These features of memantine explain its clinical tolerance and suitability for treatment of excitotoxicity.

The emerging involvement of aberrant synaptic function and plasticity in AD and depression provided important insights on identifying new molecular players as potential drug targets. In particular, modulators of NMDARs that facilitate synaptic transmission or LTP induction could potentially function as cognitive enhancers to limit cognitive decline in AD and depression. Interestingly, studies aimed at elucidating the mechanisms of action of memantine
reveal that excessive NMDAR activation may also impair synaptic plasticity (Parsons et al. 2007), suggesting that other NMDAR antagonists may be developed as cognitive enhancers to combat decline in cognitive functions. In light of the successful development of memantine as AD therapeutics, it is important to select for NMDAR antagonists that preserve physiological function of NMDARs. Similarly, development of positive modulators targeting AMPAR trafficking and function may also prove to be beneficial to ameliorating synaptic deficit in these disorders. On the other hand, the critical involvement of BDNF in synaptic plasticity indicates that TrkB agonists may also help to reverse synaptic deficits in AD and certain brain regions in depressed patients. Direct infusion of trophic factors such as NGF as therapeutics for neurodegenerative diseases have long attracted interest based on their neuroprotective effect. Nonetheless, inefficient crossing of the blood–brain barrier and the non-specific effect of these trophic factors have limited their applicability as therapeutics. It is therefore important to identify TrkB agonists that can cross the blood–brain barrier, in addition to developing methods that would allow precise delivery of the agonists. Interestingly, a recent study reported the identification of a small molecule BDNF mimetic that reduces neurotoxin-induced neuronal loss in vitro, in addition to restoring motor learning following traumatic brain injury (Massa et al. 2010). This observation further supports the potential therapeutic efficacy of TrkB agonists in ameliorating synaptic deficits in neurodegenerative diseases. Cdk5 inhibitors present yet another potential drug target for the development of cognitive enhancer in light of its involvement in AD pathology. In particular, since Cdk5 conditional knockout mice exhibit enhanced spatial learning (Hawasli et al. 2007), the development of Cdk5 inhibitors as therapeutics for AD will not only alleviate neuronal loss, but will also enable amelioration of disease progression by targeting synaptic dysfunction early on (Fig. 2). Collectively, these studies have identified several new molecular players that may be targeted to reverse synaptic and cognitive deficits in AD, and other disorders where synaptic impairment may be implicated. Interestingly, there has also been an increasing demand for cognitive enhancers as a lifestyle drug for healthy individuals. While the ethical issues related to the consumption of cognitive enhancers remain a debated topic, it is plausible that these cognitive enhancers may also benefit healthy individuals.

Finally, while novel drug targets are identified from basic research focused on elucidating the pathophysiological machinery of various neurological disorders, it is interesting to note that studies aimed at explicating the mechanism of action of existing drugs have also provided remarkable insights. For example, recent studies have revealed that neurogenesis induced by antidepressants is critical for their therapeutic effect (Krishnan & Nestler, 2008; Pittenger & Duman, 2008). Interestingly, memantine has also been recently observed to induce adult neurogenesis in the hippocampus (Maekawa et al. 2009). In light of the emerging involvement of neurogenesis in learning and memory (Deng et al. 2010), it will be important to explore if other modulators of neurogenesis may also be developed as cognitive enhancers.

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Statement of Interest

None.

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