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Targeting the Hippocampal Mossy Fiber Synapse for the Treatment of Psychiatric Disorders

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Abstract It is widely known that new neurons are continuously generated in the dentate gyrus of the hippocampus in the adult mammalian brain. This neurogenesis has been implicated in depression and antidepressant treatments. Recent evidence also suggests that the dentate gyrus is involved in the neuropathology and pathophysiology of schizophrenia and other related psychiatric disorders. Especially, abnormal neuronal development in the dentate gyrus may be a plausible risk factor for the diseases. The synapse made by the mossy fiber, the output fiber of the dentate gyrus, plays a critical role in regulating neuronal activity in its target CA3 area. The mossy fiber synapse is characterized by remarkable activity-dependent short-term synaptic plasticity that is established during the postnatal development and is supposed to be central to the functional role of the mossy fiber. Any defects, including developmental abnormalities, in the dentate gyrus and drugs acting on the dentate gyrus can modulate the mossy fiber-CA3 synaptic transmission, which may eventually affect hippocampal functions. In this paper, I review recent evidence for involvement of the dentate gyrus and mossy fiber synapse in psychiatric disorders and discuss potential importance of drugs targeting the mossy fiber synapse either directly or indirectly in the therapeutic treatments of psychiatric disorders.

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Introduction

The hippocampus has been implicated in the neuropathology of psychiatric disorders. Magnetic resonance imaging (MRI) studies have consistently demonstrated a reduction in the hippocampus volume in patients with psychiatric disorders [1–3] and functional MRI studies have shown changes in the hippocampal activity that are associated with symptoms of psychiatric disorders [4, 5]. Histological studies on the postmortem brain have revealed changes in expression of various genes in the hippocampus of the patients (see Table 1). These studies in humans have provided valuable information as to potential molecular targets for the treatment of the diseases and would also help develop an objective way to elucidate effects of ongoing treatments on the hippocampus. However, it is still poorly understood how functions of the hippocampal neurons are actually altered in the brain of patients with psychiatric disorders. In order to investigate cellular mechanisms underlying a particular disease, detailed studies using animal models would be indispensable. Despite fundamental difficulties in modeling abnormalities of human mind using experimental animals, biological approaches to psychiatric disorders that utilize animal models are getting generally accepted. In conventional pharmacological approaches, psychotropic drugs used in humans are administered to experimental animals assuming that drug-induced cellular and/or molecular changes in animal brains would be comparable to those in human brains. Accumulating evidence suggests that mice with the targeted

Table 1 Abnormalities in the dentate gyrus and mossy fiber observed in the postmortem brain of patients with schizophrenia

		Reference
Abnormalities in dentate gyrus		
Morphology	Increased frequency of dentate granule cells with basal dendrites	[149]
Neurotransmitter receptor		
Glutamate	Decrease in [^{3}H]kainate binding	[115]
	Decreases in AMPA receptor subunit GluR1 and GluR2 mRNAs (no significant change in CA1)	[116]
	Decrease in kainate receptor subunits GluR6 and KA2 mRNAs (no significant change in CA1)	[117]
	Decrease in NMDAR receptor subunit NR1mRNAs (no significant change in CA1)	[118, 120]
Acetylcholine	Decrease in [^{125}I]-α-bungarotoxin (nicotinic ligand) binding (no significant change in CA1)	[121]
	Decrease in [^{3}H]pirenzepine (muscarinic ligand) binding	[122]
GABA	Increase in [^{3}H]muscimol ($GABA_A$ ligand) binding	[113]
	Decrease in $GABA_B$ immunoreactive cells	[119]
Noradrenaline	Decrease in [^{125}I]iodopindolol (βreceptor ligand) binding	[114]
Hormone receptor	Decrease in glucocorticoid receptor mRNA	[191]
	Decrease in estrogen receptor α mRNA (dentate gyrus-specific change)	[192]
Presynaptic protein	Decrease in synaptophysin immunoreactivity (no significant change in CA1)	[123]
	Increase in synaptophysin immunoreactivity	[124]
	Decrease in SNAP-25 immunoreactivity	[124]
Neurodevelopment/Plasticity	Decrease in PSA-NCAM immunoreactive cell in hilus	[193]
	Decrease in [^{3}H]forskolin (adenylate cyclase ligand) binding (dentate gyrus-specific change)	[194]
	Decrease in density of reelin immunoreactive cells	[136]
	Increase in retinoic acid receptor α immunoreactive granule cells	[138]
	Decrease in calbindin mRNA (laser captured dentate gyrus)	[125]
	Decrease in reelin mRNA-expressing molecular layer cells	[137]
	Decrease in cells with proliferation maker Ki-67 immunoreactivity	[75]
	Decrease in GAP-43 immunoreactivity in hilus	[195]
Other	Decrease in dysbindin-1 immunoreactivity	[135]
	Decreases in proteasome, ubiquitin, and mitochondrial gene expression (laser captured dentate gyrus)	[125]
	Decrease in dysbindin-1 mRNA (no significant change in CA1)	[129]
Abnormalities in mossy fiber		
	Decrease in Timm staining	[196]
	Decrease in chromogranin B and synapsin I immunoreactivity	[128]
	Decrease in dysbindin-1 immunoreactivity	[135]
	Change in synaptic structure	[126]
	Decrease in density of MF terminals	[127]

mutation in disease-associated genes would be valuable models for psychiatric disorders [6]. The validity of the mutant mouse model is best exemplified by the finding of association of the gene encoding a subunit of calcineurin with schizophrenia. In this case, the association was predicted based on behavioral characterization of calcineurin mutant mice [7, 8] and confirmed by human genetic studies [9–11]. Recent studies using experimental animals have proposed the critical importance of the dentate gyrus and its output, the mossy fiber, in the pathophysiology and treatment for psychiatric disorders. Especially, there is an emerging possibility that abnormalities in the functional maturation of the dentate gyrus and mossy fiber synaptic transmission are critically involved in schizophrenia and

other related psychiatric disorders. It should be noted that this idea is partly based on observations in electrophysiological studies that revealed unique properties of the mossy fiber synapse and marked dysfunction of this synapse relevant to psychiatric disorders. In this paper, I review recent studies addressing the involvement of the dentate gyrus and mossy fiber in psychiatric disorders, mainly focusing on evidence derived from experimental animals. I start with a summary of physiological properties of the mossy fiber synapse, and discuss why dysfunction of mossy fiber can substantially affect hippocampal functions and how pharmacological treatments can modify the mossy fiber synaptic transmission.

Unique Role for Mossy Fibers in Hippocampal Neuronal Circuit

The hippocampal neuronal circuit is comprised of anatomically distinct three major areas connected by glutamatergic excitatory synapses. The dentate gyrus is positioned at the entrance of this so-called trisynaptic circuit and has been implicated in pattern separation or disambiguation of similar patterns of sensory inputs [12–15]. The principal neurons of the dentate gyrus, the granule cells, have relatively low in vivo firing rates [16], which may be at least partly due to very polarized resting membrane potentials of these cells [17–20]. The axons of the granule cells, the mossy fibers, form large synaptic terminals, typically 3 to 5 μm in diameter, preferentially at the proximal apical dendrite of pyramidal cells in the CA3 region [21]. Based on the anatomical feature, the mossy fiber synapse has been theoretically hypothesized to be a "detonator" or "teacher" synapse in the CA3 network [22, 23]. This theoretical prediction was confirmed by later experimental studies, but in a slightly modified form (see below).

The mossy fiber-CA3 pyramidal cell synapse has unique physiological properties. The mossy fiber synaptic transmission has a very wide dynamic range and is strongly dependent on the presynaptic firing rate [24–26]. For example, a rise in the stimulus frequency from 0.1 or 0.05 to 1 Hz leads to an increase in the synaptic efficacy by 500% to 700% [20, 24, 27]. Activity-dependent short-term modifications of synaptic efficacy are called short-term synaptic plasticity and are mostly dependent on presynaptic mechanisms [28]. Although the short-term plasticity is generally observed in a form of either facilitation (enhancement) or depression, the magnitude of the mossy fiber synaptic facilitation, especially, the frequency facilitation described above, is exceptionally large. Due to this frequency dependence of the transmission efficacy, the mossy fiber synapse can work as a high-pass filter. Indeed, Henze et al. showed that high-frequency stimulation of the granule cells in vivo reliably evokes spiking in postsynaptic CA3 neurons, but single spikes or low-frequency stimulation is much less effective [29]. Importantly, high-frequency activation of even single granule cells is sufficient for firing postsynaptic cells [29]. Furthermore, in slice preparations, activation of putative single granule cells in high-frequency bursts provides effective postsynaptic activity for the induction of long-term potentiation (LTP) at converging non-mossy fiber inputs [30]. Therefore, the mossy fiber input can serve as a "conditional detonator" that has strong impact on activity of postsynaptic cells only during high-frequency transmission [29]. Collaterals of the mossy fibers make synaptic contacts on neurons in the hilar region [31, 32]. The hilar neurons include inhibitory interneurons and the excitatory mossy cells, which innervate the granule cells and interneurons [33, 34]. The mossy fiber-mossy cell synapse also shows large frequency facilitation and is generally similar to the mossy fiber-CA3 pyramidal cell synapse [35]. The magnitude of the frequency facilitation at the mossy fiber-CA3 synapse increases with postnatal development and reaches the adult level in 3 to 4 weeks [27]. The somatic properties of the granule cells also change with development. Immature granule cells are more easily excited by somatic current injection than mature granule cells. However, repetitive spiking can be evoked in mature granule cell, but not in immature cells [18, 19]. Therefore, the dentate-to-CA3 neuronal system develops into the mature state that is suitable for transmitting high-frequency signaling (Fig. 1).

Long-term plasticity has also been demonstrated at the mossy fiber synapse. In most excitatory synapses in the hippocampus, the induction of long-term synaptic plasticity requires coincident pre- and postsynaptic activities and the

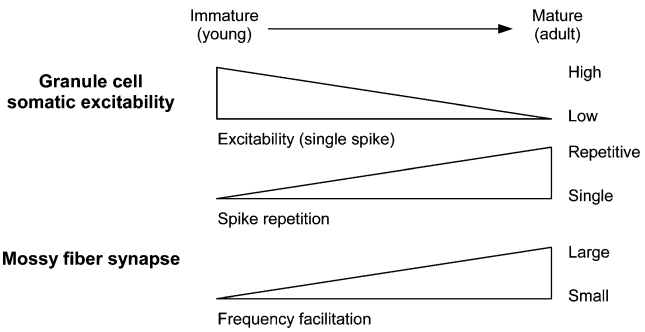

Fig. 1 Developmental changes in physiological properties of the granule cell soma and mossy fiber synapse. Immature granule cells are more easily excited than mature cells by somatic current injection (*top*). However, sustained current injection can evoke repetitive action potentials in mature granule cell, but not in immature cells (*middle*). The frequency facilitation of the mossy fiber synaptic transmission increases with development (*bottom*). Therefore, mature granule cells can much more effectively transmit high-frequency signaling than immature granule cells

resultant activation of *N*-methyl-D-aspartate (NMDA) subtypes of glutamate receptors [36]. However, at the mossy fiber synapse, neither NMDA receptors nor postsynaptic depolarization is required for LTP [37–40; but see 41–43] or long-term depression [24, 44; but see 45]. Therefore, presynaptic firing patterns primarily regulate the efficacy of the mossy fiber synapse in both short and long terms.

The mossy fiber synaptic transmission is also regulated by various neurotransmitters. Glutamate autoreceptors play a variety of roles in both short- and long-term plasticity [46–48; reviewed by 49]. Endogenous opioids can be released from mossy fiber terminals during high-frequency firing and regulate the induction of mossy fiber LTP [50]. This opioid-mediated modulation is impaired after chronic morphine treatments [51]. Ambient adenosine has been shown to continuously and strongly inhibit the mossy fiber synaptic transmission. In the absence of the adenosine-mediated tonic inhibition, the synaptic efficacy is greatly increased and the short-term plasticity is suppressed [52; but see 53]. Therefore, a change in extracellular adenosine concentrations in pathological conditions such as ischemia and epilepsy [54] would substantially affect the mossy fiber synaptic transmission and the CA3 circuit activity. The mossy fibers transmit sub-threshold "analog" signals as well as action potentials [55]. Since the sub-threshold depolarization in the granule cell soma can enhance the action potential-mediated transmitter release from the mossy fiber terminals [55], modulations of the somatodendritic membrane conductance, such as tonic inhibition by γ-aminobutylic acid [56], would be also important in regulating the mossy fiber synaptic transmission. Recently, it has been demonstrated that the mossy fiber synaptic transmission is potentiated by dopamine [57, 58] and serotonin [59]. Noradrenaline has been shown to modulate the induction of LTP without affecting the basal transmission [60]. The serotonergic modulation of the mossy fiber synapse is a plausible target for antidepressant drugs (see below). It should be noted that all these monoaminergic modulations of the mossy fiber synapse are mediated by activation of Gs-coupled receptors. The mossy fiber synapse is highly sensitive to intracellular cAMP concentrations. An adenylate cyclase activator, forskolin, induces marked potentiation of the synaptic transmission [58, 59, 61], and an inhibitor of phosphodiesterase that catalyzes cAMP hydrolysis augments the synaptic transmission and the monoaminergic modulations [58, 59]. Cyclic AMP signaling pathways have been implicated in antidepressant and ntipsychotic effects. Phosphodiesterase inhibitors have been shown to have antidepressant-like [62] and antipsychotic-like effects [63, 64]. The intracellular pathways as well as the receptors involved in the mossy fiber synaptic modulations would be potential targets for treatments of psychiatric disorders.

Effects of Antidepressants on Dentate Gyrus and Mossy Fiber Synapse

It is generally accepted that new neurons are continuously generated in the dentate gyrus of the adult brain. The adult neurogenesis has been demonstrated in various mammalian species including humans [reviewed by 65]. Newly generated neurons can be functionally integrated into the existing neuronal circuits [66–68]. In experimental animals, the adult neurogenesis in the dentate gyrus is increased by chronic administration of antidepressant drugs including tricyclic antidepressant drugs, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors [69–71]. Electroconvulsive stimulation (ECS), an experimental model of electroconvulsive therapy for depression, also increases the adult neurogenesis [69]. Chronic treatment with fluoxetine, a widely used SSRI, can stimulate the maturation of newly generated neurons [72]. Since various forms of stress can depress the adult neurogenesis, it has been hypothesized that the adult neurogenesis is involved both in the pathogenesis of depression and in antidepressant effects [reviewed by 73]. Indeed, ablation of the proliferation of neuronal progenitor cells in the adult hippocampus by x-irradiation prevents behavioral effects of antidepressant drugs [70, 71, 74]. However, x-irradiation itself neither increased depression-related behaviors nor affected stress-induced changes in behaviors. Furthermore, x-irradiation does not prevent antidepressant-like effects of a corticotropin-releasing factor 1 antagonist or a vasopressin 1b antagonist [74]. Therefore, the intact cytogenesis in the dentate gyrus does not seem to be essential for depression-related behaviors themselves, but is likely required for some of the behavioral effects of antidepressant drugs. Although the facilitatory effects of antidepressants on the adult neurogenesis have been consistently demonstrated in animal studies, so far there has been no clear evidence for the involvement of the neurogenesis in either depression or antidepressant actions in humans [75].

Antidepressant treatments generally increase mRNA levels of brain-derived neurotrophic factor (BDNF) in the hippocampus [reviewed by 76]. BDNF is abundantly expressed in the dentate gyrus and along the mossy fiber pathway [77, 78]. A recent study demonstrated that the selective deletion of BDNF in the dentate gyrus suppresses behavioral effects of subchronic antidepressant treatments [79], further supporting the importance of the dentate gyrus in antidepressant effects. In the postmortem human brain, an increase in BDNF protein levels was found in the dentate gyrus of subjects treated with antidepressant medications at the time of death, compared with antidepressant-untreated subjects [80]. In experimental animals, ECS consistently increases BDNF protein as well as mRNA levels [81–83]. However, after pharmacological antidepres-

sant treatments, hippocampal BDNF protein levels are not significantly changed [81, 83, 84], decreased [82], or increased only in the hippocampus proper, but not in the dentate gyrus [85]. Interpretation of these results are further complicated by the fact that proBDNF, from which mature BDNF was processed, can also be secreted and work as a signaling molecule with distinct actions [86–88]. In order to understand a role for BDNF in antidepressant actions, changes in protein levels of both mature and proBDNF after antidepressant treatments have to be elucidated.

Given the importance of the dentate gyrus in antidepressants actions, one might expect that antidepressant treatments also affect the mossy fiber system. However, so far only a few studies have addressed this issue. Repeated ECS induces sprouting of mossy fibers [89–91], but antidepressant drug treatments do not [91]. The ability of ECS to induce mossy fiber sprouting might be related to the superiority of the electroconvulsive therapy in effectiveness against depression as compared with antidepressant drugs [92]. However, the clinical significance of the ECS-induced sprouting remains to be elucidated. Recently, Kobayashi et al. showed that chronic administration of fluoxetine causes robust changes in the serotonergic modulation of the mossy fiber synaptic transmission in mice [59]. Serotonin (5-hydroxytriptamine (5-HT)) potentiates the mossy fiber synaptic transmission via activation of 5-HT_4 receptors. Chronic fluoxetine reduced the synaptic potentiation induced by higher concentrations of 5-HT but enhanced that induced at lower concentrations, which represents the stabilization of the serotonergic modulation (see Fig. 2). The reduction and enhancement of the serotonergic modulation by chronic fluoxetine could be explained by downregulation of the 5-HT transporter and by desensitization/downregulation of 5-HT_4 receptors or downstream effectors, respectively. Chronic antidepressant treatments reduce effects of a synthetic 5-HT_4 agonist on excitability of hippocampal pyramidal cells [93, 94]. The desensitization or downregulation of 5-HT receptors by antidepressant treatments has been demonstrated in other brain regions both in experimental animals and humans [reviewed by 95, 96]. The downregulation of the serotonin transporter after chronic SSRI treatments can be seen in whole brain regions [97, 98]. Therefore, it is possible that the bidirectional modulation or stabilization of the serotonergic modulation can be generally induced by chronic SSRI treatments. While the clinical significance of the stabilizing action is unknown, the effect of chronic fluoxetine on the mossy fiber synapse is associated with reduced locomotor activity of mice in novel environments [59], suggesting that the stabilization can contribute to the suppression of excess reactivity to external stimuli.

The serotonergic stabilizing effects of chronic fluoxetine described above may not be due to either facilitation of the adult neurogenesis or changes in BDNF expression. The facilitation of the adult neurogenesis may increase the proportion and the number of young granule cells, which could then change functions of the dentate gyrus. Chronic SSRI treatments have been shown to reduce expression of calbindin, a marker for mature granule cells, in the hippocampus [99, 100]. Newly generated granule cells exhibit enhanced LTP only between 1 and 1.5 months of the cell age [101]. The chronic fluoxetine treatment indeed causes the enhancement of LTP at the perforant path-granule cell synapse that is blocked by x-irradiation [72; but see 102]. The enhanced neurogenesis may also affect the mossy fiber synaptic transmission, since the functional properties of the mossy fiber synapse change with development [26, 27]. BDNF is required for the develop-

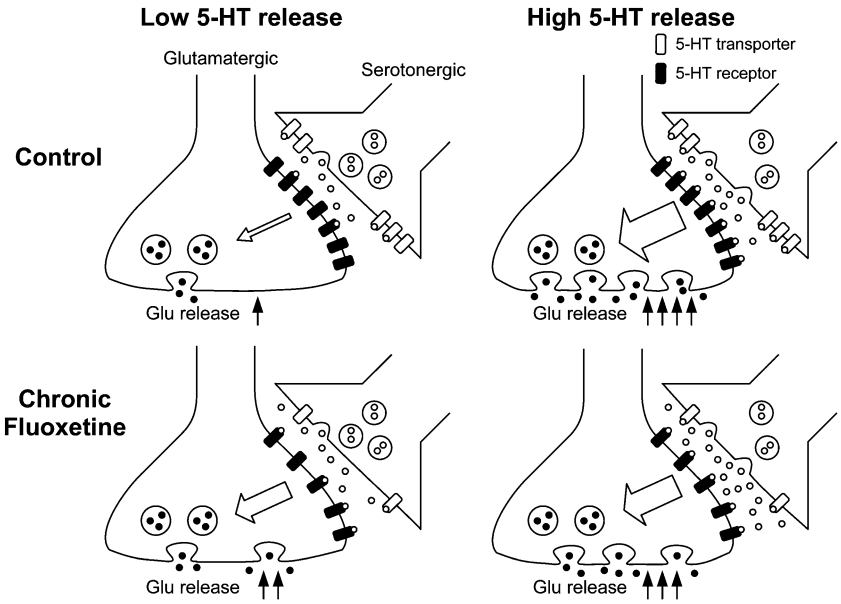

Fig. 2 Possible mechanisms underlying stabilizing effects of chronic fluoxetine on serotonergic modulations. Assume that 5-HT facilitates glutamate release by activating presynaptic 5-HT receptors. Downregulation and/or block of 5-HT transporter by fluoxetine increase extracellular 5-HT concentrations. Downregulation of 5-HT receptors and/or modulation of downstream signaling reduce effects of 5-HT on the glutamate release. These changes can lead to stabilization of the serotonergic modulation

ment of the dentate gyrus [103] and has been shown to acutely affect CA3 population spikes evoked by mossy fiber stimulation [104]. Therefore, chronic antidepressant treatments may also affect intrinsic properties of the mossy fiber synaptic transmission in addition to the serotonergic modulation. A preliminary study suggests that chronic fluoxetine at relatively high doses reduces the mossy fiber synaptic facilitation in adult mice [105]. Although this result is consistent with the idea that chronic fluoxetine increases the proportion of young granule cells, this issue largely remains to be elucidated.

Involvement of Dentate Gyrus and Mossy Fiber in Neuropathology and Pathophysiology of Schizophrenia

The hippocampus has been implicated in schizophrenia [reviewed by 106, 107]. MRI studies have shown reduced hippocampal size in patients with schizophrenia [1, 3]. Since the hippocampus plays an important role in working memory [13] and prepulse inhibition [108], which are impaired in patients with schizophrenia [109, 110], it is highly likely that hippocampal dysfunction can cause some of symptoms seen in schizophrenia. In experimental animals, selective lesions of the dentate gyrus by colchicine have been shown to impair working memory [111, 112]. Studies on the postmortem brain revealed substantial abnormalities in the dentate gyrus in patients with schizophrenia (Table 1). Those include changes in expression of various transmitter receptors [113–122], other synaptic proteins [123, 124], and proteasome, ubiquitin, and mitochondrial genes [125], suggesting profound functional defects of the dentate gyrus in schizophrenia. The mossy fiber system also has some abnormalities in synaptic structure [126], density of synaptic terminals [127], and expression of presynaptic proteins [128]. It is worth noting that some of these changes are relatively specific to the dentate gyrus, but not observed in CA1 (see Table 1), as represented by a decease in expression of the dysbindin-1 (*DTNBP1*) gene [129]. *DTNBP1* is one of the most promising schizophrenia susceptibility genes [130] and mice with a deletion in the *DTNBP1* gene show impairment in working memory [131]. Dysbindin-1 has been shown to regulate release of glutamate neurotransmitter [132, 133]. Intense dysbindin-1-like immunoreactivity is seen in the mossy fiber terminal area and the dentate inner molecular layer in humans [134, 135]. This dysbindin-1-like immunoreactivity is strongly reduced in schizophrenia [135], raising the possibility that the mossy fiber synaptic transmission is impaired in patients with schizophrenia. It should also be noted that there are abnormalities related to neuronal development and maturation such as reduced neural progenitor cell proliferation [75], reduced density of reelin positive cells [136, 137], increased expression of retinoic acid receptor α [138], and reduced expression of the mature granule cell marker calbindin [125]. Abnormal neurodevelopment has been implicated in the pathogenesis of schizophrenia [139]. Therefore, it is possible that the dentate gyrus of schizophrenic patients fails to develop into the proper mature state.

Studies in experimental animals support this hypothesis. The *NPAS3* (neuronal PAS domain protein 3) gene has been shown to be disrupted by chromosomal translocation in a family with schizophrenia [140]. Mice lacking NPAS3 exhibit hyperactivity [141] and greatly reduced adult neurogenesis in the dentate gyrus [142]. *Disrupted-in-Schizophrenia 1* (*DISC1*) is one of the most plausible schizophrenia susceptibility genes [130]. DISC1 is abundantly expressed in the hippocampus throughout the embryonic and postnatal development [143, 144]. In the adult forebrain, DISC1 expression is more localized than in embryo, with the most prominent expression in the dentate granule cells [143–146]. DISC1 is also strongly expressed in the dentate granule cells of the adult human brain [147]. Virus-mediated knockdown of DISC1 in newly generated granule cells in adult mice causes mispositioning of the cell, accelerated dendritic development, and formation of basal dendrites that are not usually seen in rodents [148]. The formation of basal dendrites resembles morphological changes observed in patients with schizophrenia [149]. The DISC1 knockdown also impairs targeting of the mossy fibers, accelerates the development of mossy fiber synaptic boutons, and hampers full morphological maturation in some boutons [150]. Furthermore, a mutation in *DISC1* that models a schizophrenic risk allele impairs dendritic growth during the postnatal development of the granule cells [151]. These results are consistent with the hypothesis that the development or maturation of the dentate gyrus is impaired in schizophrenia. As described above, the remarkable frequency facilitation at the mossy fiber synapse is established during the postnatal development [27] and somatic properties of the granule cells also strongly depend on the developmental stage of the cell [17–19] (see Fig. 1). Therefore, these synaptic and somatic properties are supposed to be altered in the dentate gyrus with abnormalities in development and possibly in the brain of patients with schizophrenia. A recent study on mice heterozygous for alpha-calcium and calmodulin-dependent protein kinase II (alpha-CaMKII +/− mice) provided a strong support for this idea [20]. Alpha-CaMKII +/− mice show profound behavioral abnormalities including hyperactivity, a severe working memory deficit, and an exaggerated infradian rhythm, which are related to symptoms in schizophrenia and other psychiatric disorders. In the dentate gyrus of the mutant mice, the granule cells have less developed dendritic arborization. The expression of calbindin is largely suppressed, while markers for immature granule cells are

increased. As expected, the physiological properties of the mutant granule cells are strikingly similar to those of immature granule cells. Thus, the magnitude of mossy fiber synaptic facilitation is strongly reduced, and somatic spikes are easily evoked, but reduced in number during sustained depolarization. Analysis of the gene expression of the postmortem human hippocampus using biomarkers that characterize the mutant hippocampus suggested similarities in gene expression patterns between alpha-CaMKII +/− mice and patients with schizophrenia, which include the reduction of calbindin expression [20]. Another piece of evidence for the present hypothesis was provided by studies on mice lacking the kainite receptor subunit GluR6. GluR6 is essential for the large facilitation of the mature mossy fiber synapse [27, 152, 153]. The GluR6-deficient mice show severe behavioral abnormalities including hyperactivity and increased responsiveness to psychostimulants, which are related to mania or psychosis [154]. Consistently, in the postmortem brain of schizophrenic patients, the expression of GluR6 mRNA is reduced in the dentate gyrus and CA3 region [117]. Taken together, these lines of evidence suggest that dysfunction of the mossy fiber synapse associated with abnormalities in the granule cell maturation is involved in the pathophysiology of schizophrenia and/or other related psychiatric disorders. The abnormalities in the dentate gyrus and mossy fiber may be part of the neuropathology of schizophrenia. However, the dentate gyrus may be particularly susceptible to developmental problems due to the continuous postnatal neurogenesis, and the developmental defects of the dentate gyrus could be functionally expressed in an exaggerated form as changes in the large synaptic facilitation at the mossy fiber synapse, thereby substantially contributing to the pathophysiology of schizophrenia.

Most of the animal studies described above have been carried out using rodents. In addition to difficulties in modeling psychiatric disorders using experimental animals in general, marked differences in the brain anatomy, such as the relative hippocampal size, between rodents and primates would pose a problem in extrapolating results of rodent studies to humans. There are some important differences in the anatomy of the dentate gyrus between rodents and primates. A subpopulation of the mature granule cells has basal dendrites in primates, but not in rodents [155]. The distribution of the mossy fibers is significantly different among species [156]. It is not known whether these anatomical differences are accompanied by functional differences. Mossy fiber LTP in cynomolgus monkeys has been shown to be independent of NMDA receptors as in rodents [157]. Some other studies also report similarities in synaptic and somatic membrane properties of the granule cells between rodents and nonhuman primates [158, 159]. Further cellular physiological studies in nonhuman primates would be important to clarify the involvement of the dentate gyrus and mossy fibers in psychiatric disorders.

Effects of Antipsychotic Drugs on Dentate Gyrus and Mossy Fiber Synapse

In contrast to a lot of literature regarding antidepressant effects, effects of antipsychotic drugs on the dentate gyrus in experimental animals have not been addressed in detail. Typical and atypical antipsychotic drugs cause a decrease and increase in BDNF mRNA levels, respectively [160]. Typical antipsychotic drugs increase levels of the presynaptic protein SNAP-25 in hippocampal synaptic regions with the strongest effect at the mossy fiber pathway [161]. Some antipsychotic drugs can increase cell proliferation in the dentate gyrus [reviewed by 162]. Atypical antipsychotic drugs have been shown to facilitate the adult neurogenesis in the dentate gyrus in some studies [163, 164] but have no significant effects in others [165–168]. The discrepancies in reported effects might be due to methodological differences. Haloperidol, a typical antipsychotic drug, has no effects on the neurogenesis in rats [69, 163, 165, 167–169] but facilitates the neurogenesis in gerbil [170]. Thus, the adult neurogenesis in the dentate gyrus might be involved in some actions of antipsychotic drugs. Since the adult neurogenesis is modulated by atypical, but not by typical, antipsychotic drugs in rats, it may be associated with negative symptoms of schizophrenia, on which atypical antipsychotic drugs generally have superior therapeutic effects as compared with typical antipsychotics [171]. Ameliorating effects of antipsychotic drugs on positive or psychotic symptoms have been ascribed to their antagonistic actions on dopamine D_2 or D_3 receptors [172]. Activation of D_2-like receptors by exogenous agonists increases the adult neurogenesis in the hippocampus [173, 174], which may be mediated by ciliary neurotrophic factor released from astrocytes [174]. The lack of effects of the highly potent D_2 antagonist haloperidol on the neurogenesis suggests that endogenous dopamine does not activate this D_2-dependent pathway for the regulation of the adult neurogenesis in a normal condition. Since overactivation of astrocytes has been suggested in schizophrenia [175], this pathway might be endogenously activated in the pathological condition. In the postmortem brain of patients with schizophrenia, the neural progenitor cell proliferation in the dentate gyrus has been shown to be reduced [75]. However, most subjects in this study received antipsychotic drugs, which may complicate interpretation of the results.

Although effects of currently utilized antipsychotic drugs on the mossy fiber synapse have not been well investigated, this synapse can be a potential target of recently developed candidate antipsychotic drugs. A metabotropic glutamate 2/3 receptor (mGluR2/3) agonist has been shown to have

antipsychotic actions both in animal studies [176] and in a clinical trial [177]. Activation of mGluR2/3 strongly suppresses the mossy fiber synaptic transmission via presynaptic mechanisms [46, 178], but other hippocampal synapses are either insensitive or less sensitive to mGluR2/3 agonists [178, 179]. Therefore, mGluR2/3 agonists at optimal doses would preferentially inhibit signaling via the dentate gyrus-mossy fiber pathway in the hippocampal circuit. The synaptic facilitation increases along with the synaptic inhibition caused by mGluR2/3 activation [178]. Therefore, mGluR2/3 agonists may be effective in treating the reduced mossy fiber synaptic facilitation associated with abnormalities in the dentate gyrus maturation.

A partial agonist of α7 neuronal nicotinic acetylcholine receptors has also been shown to ameliorate some symptoms of schizophrenia [180, 181]. The α7 nicotinic receptor gene, *CHRNA7*, is one of the candidate genes for schizophrenia [182]. Alpha7 nicotinic receptors are highly expressed in the hippocampus, especially in the hilar region [183]. In the dentate gyrus of patients with schizophrenia, binding of α-bungarotoxin, a blocker of α7 neuronal nicotinic receptors, is reduced [121]. Mice lacking α7 nicotinic receptors exhibit impairment in attention [184] and working or episodic-like memory [185]. Application of nicotine induces a rise in calcium concentrations in the mossy fiber terminals and increases action potential-independent release of neurotransmitter probably via activation of α7 nicotinic receptors [186–188; but see 189]. It is possible that modulation of mossy fiber synaptic transmission by α7 agonists can contribute to improvement of cognitive functions.

Conclusions: Mossy Fiber Synapse as a Target for Treatments of Psychiatric Disorders

Since the mossy fiber synapse plays critical roles in regulating excitability and plasticity in the CA3 circuit, dysfunction of this synapse would substantially affect functions of the hippocampus. Various neurotransmitter receptors at the mossy fiber synapse can be potential targets for pharmacological treatments of psychiatric disorders. Abnormal development or maturation of the dentate granule cells likely contributes to the pathophysiology of schizophrenia and other related psychiatric disorders. Dysfunction of the mossy fiber synaptic transmission could be secondary to the abnormalities in the granule cells maturation. In this case, drugs that directly act on the mossy fiber synapse may ameliorate or control a part of symptoms but may not afford a complete cure of the disorder. Instead, drugs that are expected to affect neuronal maturation or differentiation such as retinoic acid analogs might be effective in treating such defects [190]. It would also be important to reevaluate currently utilized antipsychotic drugs with respect to possible efficacy in alleviating the dysfunction associated with maturational or developmental defects of the dentate gyrus, thereby indirectly modulating the mossy fiber synaptic transmission. Genetically manipulated mice such as alpha-CaMKII +/− mice as well as conventional schizophrenia model animals would be valuable tools for re-evaluation of current psychotropic drugs and screening of candidate drugs.

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References

1. Lawrie SM, Abukmeil SS (1998) Brain abnormality in schizophrenia. A systematic and quantitative review of volumetric magnetic resonance imaging studies. Br J Psychiatry 172:110–120
2. Videbech P, Ravnkilde B (2004) Hippocampal volume and depression: a meta-analysis of MRI studies. Am J Psychiatry 161:1957–1966
3. Steen RG, Mull C, McClure R, Hamer RM, Lieberman JA (2006) Brain volume in first-episode schizophrenia: systematic review and meta-analysis of magnetic resonance imaging studies. Br J Psychiatry 188:510–518
4. Shergill SS, Brammer MJ, Williams SCR, Murray RM, McGuire PK (2000) Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch Gen Psychiatry 57:1033–1038
5. Oertel V, Rotarska-Jagiela A, van de Ven VG, Haenschel C, Maurer K, Linden DEJ (2007) Visual hallucinations in schizophrenia investigated with functional magnetic resonance imaging. Psychiatry Res 156:269–273
6. Takao K, Yamasaki N, Miyakawa T (2007) Impact of brain-behavior phenotypying of genetically-engineered mice on research of neuropsychiatric disorders. Neurosci Res 58:124–132
7. Zeng H, Chattarji S, Barbarosie M, Rondi-Reig L, Philpot BD, Miyakawa T, Bear MF, Tonegawa S (2001) Forebrain-specific calcineurin knockout selectively impairs bidirectional synaptic plasticity and working/episodic-like memory. Cell 107:617–629
8. Miyakawa T, Leiter LM, Gerber DJ, Gainetdinov RR, Sotnikova TD, Zeng H, Caron MG, Tonegawa S (2003) Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. Proc Natl Acad Sci USA 100:8987–8992
9. Gerber DJ, Hall D, Miyakawa T, Demars S, Gogos JA, Karayiorgou M, Tonegawa S (2003) Evidence for association of schizophrenia with genetic variation in the 8p21.3 gene, *PPP3CC*, encoding the calcineurin gamma subunit. Proc Natl Acad Sci USA 100:8993–8998
10. Horiuchi Y, Ishiguro H, Koga M, Inada T, Iwata N, Ozaki N, Ujike H, Muratake T, Someya T, Arinami T (2007) Support for association of the *PPP3CC* gene with schizophrenia. Mol Psychiatry 12:891–893
11. Liu YL, Fann CSJ, Liu CM, Chang CC, Yang WC, Hung SI, Yu SL, Hwang TJ, Hsieh MH, Liu CC, Tsuang MM, Wu JY, Jou YS, Faraone SV, Tsuang MT, Chen WJ, Hwu H-G (2007) More evidence supports the association of PPP3CC with schizophrenia. Mol Psychiatry 12:966–974
12. O'Reilly RC, McClelland JL (1994) Hippocampal conjunctive encoding, storage, and recall: avoiding a trade-off. Hippocampus 4:661–682

13. Kesner RP, Gilbert PE, Wallenstein GV (2000) Testing neural network models of memory with behavioral experiments. Curr Opin Neurobiol 10:260–265
14. Gilbert PE, Kesner RP, Lee I (2001) Dissociating hippocampal subregions: a double dissociation between dentate gyrus and CA1. Hippocampus 11:626–636
15. Leutgeb JK, Leutgeb S, Moser M-B, Moser EI (2007) Pattern separation in the dentate gyrus and CA3 of the hippocampus. Science 315:961–966
16. Jung MW, McNaughton BL (1993) Spatial selectivity of unit activity in the hippocampal granular layer. Hippocampus 3:165–182
17. Liu X-S, Tilwalli S, Ye G-l, Lio PA, Pasternak JF, Trommer BL (2000) Morphologic and electrophysiologic maturation in developing dentate gyrus granule cells. Brain Res 856:202–212
18. Ambrogini P, Lattanzi D, Ciuffoli S, Agostini D, Bertini L, Stocchi V, Santi S, Cuppini R (2004) Morpho-functional characterization of neuronal cells at different stages of maturation in granule cell layer of adult rat dentate gyrus. Brain Res 1017:21–31
19. Schmidt-Hieber C, Jonas P, Bischofberger J (2004) Enhanced synaptic plasticity in newly generated granule cells of the adult hippocampus. Nature 429:184–187
20. Yamasaki N, Maekawa M, Kobayashi K, Kajii Y, Maeda J, Soma M, Takao K, Tanda K, Ohira K, Toyama K, Kanzaki K, Fukunaga K, Sudo Y, Ichinose H, Ikeda M, Iwata N, Ozaki N, Suzuki H, Higuchi M, Suhara T, Yuasa S, Miyakawa T (2008) Alpha-CaMKII deficiency causes immature dentate gyrus, a novel candidate endophenotype of psychiatric disorders. Mol Brain 1:6
21. Amaral DG, Dent JA (1981) Development of the mossy fibers of the dentate gyrus: I. A light and electron microscopic study of the mossy fibers and their expansions. J Comp Neurol 195:51–86
22. McNaughton BL, Morris RGM (1987) Hippocampal synaptic enhancement and information storage within a distributed memory system. Trends Neurosci 10:408–415
23. Rolls ET, Treves A (1998) Neural networks and brain function. Oxford University Press, New York, pp 95–135
24. Kobayashi K, Manabe T, Takahashi T (1996) Presynaptic long-term depression at the hippocampal mossy fiber-CA3 synapse. Science 273:648–650
25. Salin PA, Scanziani M, Malenka RC, Nicoll RA (1996) Distinct short-term plasticity at two excitatory synapses in the hippocampus. Proc Natl Acad Sci USA 93:13304–13309
26. Mori-Kawakami F, Kobayashi K, Takahashi T (2003) Developmental decrease in synaptic facilitation at the mouse hippocampal mossy fibre synapse. J Physiol 553:37–48
27. Marchal C, Mulle C (2004) Postnatal maturation of mossy fibre excitatory transmission in mouse CA3 pyramidal cells: a potential role for kainate receptors. J Physiol 561:27–37
28. Zucker RS, Regehr WG (2002) Short-term synaptic plasticity. Annu Rev Physiol 64:355–405
29. Henze DA, Wittner L, Buzsáki G (2002) Single granule cells reliably discharge targets in the hippocampal CA3 network *in vivo*. Nat Neurosci 5:790–795
30. Kobayashi K, Poo M-m (2004) Spike train timing-dependent associative modification of hippocampal CA3 recurrent synapses by mossy fibers. Neuron 41:445–454
31. Claiborne BJ, Amaral DG, Cowan WM (1986) A light and electron microscopic analysis of the mossy fibers of the rat dentate gyrus. J Comp Neurol 246:435–458
32. Scharfman HE, Kunkel DD, Schwartzkroin PA (1990) Synaptic connections of dentate granule cells and hilar neurons: results of paired intracellular recordings and intracellular horseradish peroxidase injections. Neuroscience 37:693–707
33. Amaral DG (1978) A Golgi study of cell types in the hilar region of the hippocampus in the rat. J Comp Neurol 182:851–914
34. Scharfman HE (1995) Electrophysiological evidence that dentate hilar mossy cells are excitatory and innervate both granule cells and interneurons. J Neurophysiol 74:179–194
35. Lysetskiy M, Földy C, Soltesz I (2005) Long- and short-term plasticity at mossy fiber synapses on mossy cells in the rat dentate gyrus. Hippocampus 15:691–696
36. Malenka RC, Nicoll RA (1993) NMDA-receptor-dependent synaptic plasticity: multiple forms and mechanisms. Trends Neurosci 16:521–527
37. Harris EW, Cotman CW (1986) Long-term potentiation of guinea pig mossy fiber responses is not blocked by N-methyl D-aspartate antagonists. Neurosci Lett 70:132–137
38. Zalutsky RA, Nicoll RA (1990) Comparison of two forms of long-term potentiation in single hippocampal neurons. Science 248:1619–1624
39. Ito I, Sugiyama H (1991) Roles of glutamate receptors in long-term potentiation at hippocampal mossy fiber synapses. Neuroreport 2:333–336
40. Castillo PE, Weisskopf MG, Nicoll RA (1994) The role of Ca^{2+}channels in hippocampal mossy fiber synaptic transmission and long-term potentiation. Neuron 12:261–269
41. Jaffe D, Johnston D (1990) Induction of long-term potentiation at hippocampal mossy-fiber synapses follows a Hebbian rule. J Neurophysiol 64:948–960
42. Urban NN, Barrionuevo G (1996) Induction of Hebbian and non-Hebbian mossy fiber long-term potentiation by distinct patterns of high-frequency stimulation. J Neurosci 16:4293–4299
43. Yeckel MF, Kapur A, Johnston D (1999) Multiple forms of LTP in hippocampal CA3 neurons use a common postsynaptic mechanism. Nat Neurosci 2:625–633
44. Tzounopoulos T, Janz R, Südhof TC, Nicoll RA, Malenka RC (1998) A role for cAMP in long-term depression at hippocampal mossy fiber synapses. Neuron 21:837–845
45. Lei S, Pelkey KA, Topolnik L, Congar P, Lacaille J-C, McBain CJ (2003) Depolarization-induced long-term depression at hippocampal mossy fiber-CA3 pyramidal neuron synapses. J Neurosci 23:9786–9795
46. Yokoi M, Kobayashi K, Manabe T, Takahashi T, Sakaguchi I, Katsuura G, Shigemoto R, Ohishi H, Nomura S, Nakamura K, Nakao K, Katsuki M, Nakanishi S (1996) Impairment of hippocampal mossy fiber LTD in mice lacking mGluR2. Science 273:645–647
47. Scanziani M, Salin PA, Vogt KE, Malenka RC, Nicoll RA (1997) Use-dependent increases in glutamate concentration activate presynaptic metabotropic glutamate receptors. Nature 385:630–634
48. Schmitz D, Mellor J, Nicoll RA (2001) Presynaptic kainate receptor mediation of frequency facilitation at hippocampal mossy fiber synapses. Science 291:1972–1976
49. Nicoll RA, Schmitz D (2005) Synaptic plasticity at hippocampal mossy fibre synapses. Nat Rev Neurosci 6:863–876
50. Weisskopf MG, Zalutsky RA, Nicoll RA (1993) The opioid peptide dynorphin mediates heterosynaptic depression of hippocampal mossy fibre synapses and modulates long-term potentiation. Nature 362:423–427
51. Harrison JM, Allen RG, Pellegrino MJ, Williams JT, Manzoni OJ (2002) Chronic morphine treatment alters endogenous opioid control of hippocampal mossy fiber synaptic transmission. J Neurophysiol 87:2464–2470
52. Moore KA, Nicoll RA, Schmitz D (2003) Adenosine gates synaptic plasticity at hippocampal mossy fiber synapses. Proc Natl Acad Sci USA 100:14397–14402
53. Kukley M, Schwan M, Fredholm BB, Dietrich D (2005) The role of extracellular adenosine in regulating mossy fiber synaptic plasticity. J Neurosci 25:2832–2837

54. Dunwiddie TV, Masino SA (2001) The role and regulation of adenosine in the central nervous system. Annu Rev Neurosci 24:31–55
55. Alle H, Geiger JRP (2006) Combined analog and action potential coding in hippocampal mossy fibers. Science 311:1290–1293
56. Nusser Z, Mody I (2002) Selective modulation of tonic and phasic inhibitions in dentate gyrus granule cells. J Neurophysiol 87:2624–2628
57. Kobayashi K, Ikeda Y, Suzuki H (2006) Locomotor activity correlates with modifications of hippocampal mossy fibre synaptic transmission. Eur J Neurosci 24:1867–1873
58. Kobayashi K, Suzuki H (2007) Dopamine selectively potentiates hippocampal mossy fiber to CA3 synaptic transmission. Neuropharmacology 52:552–561
59. Kobayashi K, Ikeda Y, Haneda E, Suzuki H (2008) Chronic fluoxetine bidirectionally modulates potentiating effects of serotonin on the hippocampal mossy fiber synaptic transmission. J Neurosci 28:6272–6280
60. Hopkins WF, Johnston D (1988) Noradrenergic enhancement of long-term potentiation at mossy fiber synapses in the hippocampus. J Neurophysiol 59:667–687
61. Weisskopf MG, Castillo PE, Zalutsky RA, Nicoll RA (1994) Mediation of hippocampal mossy fiber long-term potentiation by cyclic AMP. Science 265:1878–1882
62. O'Donnell JM, Zhang H-T (2004) Antidepressant effects of inhibitors of cAMP phosphodiesterase (PDE4). Trends Pharmacol Sci 25:158–163
63. Maxwell CR, Kanes SJ, Abel T, Siegel SJ (2004) Phosphodiesterase inhibitors: a novel mechanism for receptor-independent antipsychotic medications. Neuroscience 129:101–107
64. Siuciak JA, Chapin DS, McCarthy SA, Martin AN (2007) Antipsychotic profile of rolipram: efficacy in rats and reduced sensitivity in mice deficient in the phosphodiesterase-4B (PDE4B) enzyme. Psychopharmacology (Berl) 192:415–424
65. Gould E, Tanapat P, Hastings NB, Shors TJ (1999) Neurogenesis in adulthood: a possible role in learning. Trends Cogn Sci 3:186–192
66. van Praag H, Schinder AF, Christie BR, Toni N, Palmer TD, Gage FH (2002) Functional neurogenesis in the adult hippocampus. Nature 415:1030–1034
67. Jessberger S, Kempermann G (2003) Adult-born hippocampal neurons mature into activity-dependent responsiveness. Eur J Neurosci 18:2707–2712
68. Toni N, Laplagne DA, Zhao C, Lombardi G, Ribak CE, Gage FH, Schinder AF (2008) Neurons born in the adult dentate gyrus form functional synapses with target cells. Nat Neurosci 11:901–907
69. Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. J Neurosci 20:9104–9110
70. Santarelli L, Saxe M, Gross C, Surget A, Battaglia F, Dulawa S, Weisstaub N, Lee J, Duman R, Arancio O, Belzung C, Hen R (2003) Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 301:805–809
71. Airan RD, Meltzer LA, Roy M, Gong Y, Chen H, Deisseroth K (2007) High-speed imaging reveals neurophysiological links to behavior in an animal model of depression. Science 317:819–823
72. Wang J-W, David DJ, Monckton JE, Battaglia F, Hen R (2008) Chronic fluoxetine stimulates maturation and synaptic plasticity of adult-born hippocampal granule cells. J Neurosci 28:1374–1384
73. Warner-Schmidt JL, Duman RS (2006) Hippocampal neurogenesis: opposing effects of stress and antidepressant treatment. Hippocampus 16:239–249
74. Surget A, Saxe M, Leman S, Ibarguen-Vargas Y, Chalon S, Griebel G, Hen R, Belzung C (2008) Drug-dependent requirement of hippocampal neurogenesis in a model of depression and of antidepressant reversal. Biol Psychiatry 64:293–301
75. Reif A, Fritzen S, Finger M, Strobel A, Lauer M, Schmitt A, Lesch K-P (2006) Neural stem cell proliferation is decreased in schizophrenia, but not in depression. Mol Psychiatry 11:514–522
76. Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. Biol Psychiatry 59:1116–1127
77. Conner JM, Lauterborn JC, Yan Q, Gall CM, Varon S (1997) Distribution of brain-derived neurotrophic factor (BDNF) protein and mRNA in the normal adult rat CNS: evidence for anterograde axonal transport. J Neurosci 17:2295–2313
78. Smith MA, Zhang L-X, Lyons WE, Mamounas LA (1997) Anterograde transport of endogenous brain-derived neurotrophic factor in hippocampal mossy fibers. Neuroreport 8:1829–1834
79. Adachi M, Barrot M, Autry AE, Theobald D, Monteggia LM (2008) Selective loss of brain-derived neurotrophic factor in the dentate gyrus attenuates antidepressant efficacy. Biol Psychiatry 63:642–649
80. Chen B, Dowlatshahi D, MacQueen GM, Wang J-F, Young LT (2001) Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. Biol Psychiatry 50:260–265
81. Altar CA, Whitehead RE, Chen R, Wörtwein G, Madsen TM (2003) Effects of electroconvulsive seizures and antidepressant drugs on brain-derived neurotrophic factor protein in rat brain. Biol Psychiatry 54:703–709
82. Jacobsen JPR, Mørk A (2004) The effect of escitalopram, desipramine, electroconvulsive seizures and lithium on brain-derived neurotrophic factor mRNA and protein expression in the rat brain and the correlation to 5-HT and 5-HIAA levels. Brain Res 1024:183–192
83. Balu DT, Hoshaw BA, Malberg JE, Rosenzweig-Lipson S, Schechter LE, Lucki I (2008) Differential regulation of central BDNF protein levels by antidepressant and non-antidepressant drug treatments. Brain Res 1211:37–43
84. De Foubert G, Carney SL, Robinson CS, Destexhe EJ, Tomlinson R, Hicks CA, Murray TK, Gaillard JP, Deville C, Xhenseval V, Thomas CE, O'Neill MJ, Zetterström TSC (2004) Fluoxetine-induced change in rat brain expression of brain-derived neurotrophic factor varies depending on length of treatment. Neuroscience 128:597–604
85. Xu H, Richardson JS, Li X-M (2003) Dose-related effects of chronic antidepressants on neuroprotective proteins BDNF, Bcl-2 and Cu/Zn-SOD in rat hippocampus. Neuropsychopharmacology 28:53–62
86. Lee R, Kermani P, Teng KK, Hempstead BL (2001) Regulation of cell survival by secreted proneurotrophins. Science 294:1945–1948
87. Teng HK, Teng KK, Lee R, Wright S, Tevar S, Almeida RD, Kermani P, Torkin R, Chen Z-Y, Lee FS, Kraemer RT, Nykjaer A, Hempstead BL (2005) ProBDNF induces neuronal apoptosis via activation of a receptor complex of $p75^{NTR}$ and sortilin. J Neurosci 25:5455–5463
88. Woo NH, Teng HK, Siao C-J, Chiaruttini C, Pang PT, Milner TA, Hempstead BL, Lu B (2005) Activation of $p75^{NTR}$ by proBDNF facilitates hippocampal long-term depression. Nat Neurosci 8:1069–1077
89. Gombos Z, Spiller A, Cottrell GA, Racine RJ, Burnham WM (1999) Mossy fiber sprouting induced by repeated electroconvulsive shock seizures. Brain Res 844:28–33
90. Vaidya VA, Siuciak JA, Du F, Duman RS (1999) Hippocampal mossy fiber sprouting induced by chronic electroconvulsive seizures. Neuroscience 89:157–166
91. Lamont SR, Paulls A, Stewart CA (2001) Repeated electroconvulsive stimulation, but not antidepressant drugs, induces mossy fibre sprouting in the rat hippocampus. Brain Res 893:53–58

92. Pagnin D, de Queiroz V, Pini S, Cassano GB (2004) Efficacy of ECT in depression: a meta-analytic review. J ECT 20:13–20
93. Tokarski K, Bijak M (1996) Antidepressant-induced adaptive changes in the effects of 5-HT, 5-HT_{1A} and 5-HT_4 agonists on the population spike recorded in hippocampal CA1 cells do not involve presynaptic effects on excitatory synaptic transmission. Pol J Pharmacol 48:565–573
94. Bijak M, Tokarski K, Maj J (1997) Repeated treatment with antidepressant drugs induces subsensitivity to the excitatory effect of 5-HT_4 receptor activation in the rat hippocampus. Naunyn Schmiedebergs Arch Pharmacol 355:14–19
95. Stahl SM (1998) Mechanism of action of serotonin selective reuptake inhibitors. Serotonin receptors and pathways mediate therapeutic effects and side effects. J Affect Disord 51:215–235
96. Vaswani M, Linda FK, Ramesh S (2003) Role of selective serotonin reuptake inhibitors in psychiatric disorders: a comprehensive review. Prog Neuropsychopharmacol Biol Psychiatry 27:85–102
97. Benmansour S, Cecchi M, Morilak DA, Gerhardt GA, Javors MA, Gould GG, Frazer A (1999) Effects of chronic antidepressant treatments on serotonin transporter function, density, and mRNA level. J Neurosci 19:10494–10501
98. Benmansour S, Owens WA, Cecchi M, Morilak DA, Frazer A (2002) Serotonin clearance *in vivo* is altered to a greater extent by antidepressant-induced downregulation of the serotonin transporter than by acute blockade of this transporter. J Neurosci 22:6766–6772
99. Miller BH, Schultz LE, Gulati A, Cameron MD, Pletcher MT (2008) Genetic regulation of behavioral and neuronal responses to fluoxetine. Neuropsychopharmacology 33:1312–1322
100. Sillaber I, Panhuysen M, Henniger MSH, Ohl F, Kühne C, Pütz B, Pohl T, Deussing JM, Paez-Pereda M, Holsboer F (2008) Profiling of behavioral changes and hippocampal gene expression in mice chronically treated with the SSRI paroxetine. Psychopharmacology (Berl) 200:557–572
101. Ge S, Yang C-h, Hsu K-s, Ming G-l, Song H (2007) A critical period for enhanced synaptic plasticity in newly generated neurons of the adult brain. Neuron 54:559–566
102. Stewart CA, Reid IC (2000) Repeated ECS and fluoxetine administration have equivalent effects on hippocampal synaptic plasticity. Psychopharmacology (Berl) 148:217–223
103. Chan JP, Cordeira J, Calderon GA, Iyer LK, Rios M (2008) Depletion of central BDNF in mice impedes terminal differentiation of new granule neurons in the adult hippocampus. Mol Cell Neurosci 39:372–383
104. Scharfman HE (1997) Hyperexcitability in combined entorhinal/hippocampal slices of adult rat after exposure to brain-derived neurotrophic factor. J Neurophysiol 78:1082–1095
105. Kobayashi K, Ikeda Y, Sakai A, Suzuki H (2008) Chronic SSRI changes the maturation state of dentate granule cells. FENS Abstr 4:181.22
106. Weinberger DR (1999) Cell biology of the hippocampal formation in schizophrenia. Biol Psychiatry 45:395–402
107. Harrison PJ (2004) The hippocampus in schizophrenia: a review of the neuropathological evidence and its pathophysiological implications. Psychopharmacology (Berl) 174:151–162
108. Bast T, Feldon J (2003) Hippocampal modulation of sensorimotor processes. Prog Neurobiol 70:319–345
109. Joyce EM, Roiser JP (2007) Cognitive heterogeneity in schizophrenia. Curr Opin Psychiatry 20:268–272
110. Turetsky BI, Calkins ME, Light GA, Olincy A, Radant AD, Swerdlow NR (2007) Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. Schizophr Bull 33:69–94
111. Jeltsch H, Bertrand F, Lazarus C, Cassel J-C (2001) Cognitive performances and locomotor activity following dentate granule cell damage in rats: role of lesion extent and type of memory tested. Neurobiol Learn Mem 76:81–105
112. Hernández-Rabaza V, Barcia JA, Llorens-Martín M, Trejo JL, Canales JJ (2007) Spared place and object-place learning but limited spatial working memory capacity in rats with selective lesions of the dentate gyrus. Brain Res Bull 72:315–323
113. Benes FM, Khan Y, Vincent SL, Wickramasinghe R (1996) Differences in the subregional and cellular distribution of $GABA_A$ receptor binding in the hippocampal formation of schizophrenic brain. Synapse 22:338–349
114. Klimek V, Rajkowska G, Luker SN, Dilley G, Meltzer HY, Overholser JC, Stockmeier CA, Ordway GA (1999) Brain noradrenergic receptors in major depression and schizophrenia. Neuropsychopharmacology 21:69–81
115. Kerwin R, Patel S, Meldrum B (1990) Quantitative autoradiographic analysis of glutamate binding sites in the hippocampal formation in normal and schizophrenic brain *post mortem*. Neuroscience 39:25–32
116. Eastwood SL, McDonald B, Burnet PWJ, Beckwith JP, Kerwin RW, Harrison PJ (1995) Decreased expression of mRNAs encoding non-NMDA glutamate receptors GluR1 and GluR2 in medial temporal lobe neurons in schizophrenia. Brain Res Mol Brain Res 29:211–223
117. Porter RHP, Eastwood SL, Harrison PJ (1997) Distribution of kainate receptor subunit mRNAs in human hippocampus, neocortex and cerebellum, and bilateral reduction of hippocampal GluR6 and KA2 transcripts in schizophrenia. Brain Res 751:217–231
118. Gao X-M, Sakai K, Roberts RC, Conley RR, Dean B, Tamminga CA (2000) Ionotropic glutamate receptors and expression of *N*-methyl-D-aspartate receptor subunits in subregions of human hippocampus: effects of schizophrenia. Am J Psychiatry 157:1141–1149
119. Mizukami K, Sasaki M, Ishikawa M, Iwakiri M, Hidaka S, Shiraishi H, Iritani S (2000) Immunohistochemical localization of γ-aminobutyric $acid_B$ receptor in the hippocampus of subjects with schizophrenia. Neurosci Lett 283:101–104
120. Law AJ, Deakin JFW (2001) Asymmetrical reductions of hippocampal NMDAR1 glutamate receptor mRNA in the psychoses. Neuroreport 12:2971–2974
121. Freedman R, Hall M, Adler LE, Leonard S (1995) Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol Psychiatry 38:22–33
122. Crook JM, Tomaskovic-Crook E, Copolov DL, Dean B (2000) Decreased muscarinic receptor binding in subjects with schizophrenia: a study of the human hippocampal formation. Biol Psychiatry 48:381–388
123. Eastwood SL, Harrison PJ (1995) Decreased synaptophysin in the medial temporal lobe in schizophrenia demonstrated using immunoautoradiography. Neuroscience 69:339–343
124. Young CE, Arima K, Xie J, Hu L, Beach TG, Falkai P, Honer WG (1998) SNAP-25 deficit and hippocampal connectivity in schizophrenia. Cereb Cortex 8:261–268
125. Altar CA, Jurata LW, Charles V, Lemire A, Liu P, Bukhman Y, Young TA, Bullard J, Yokoe H, Webster MJ, Knable MB, Brockman JA (2005) Deficient hippocampal neuron expression of proteasome, ubiquitin, and mitochondrial genes in multiple schizophrenia cohorts. Biol Psychiatry 58:85–96
126. Kolomeets NS, Orlovskaya DD, Rachmanova VI, Uranova NA (2005) Ultrastructural alterations in hippocampal mossy fiber synapses in schizophrenia: a postmortem morphometric study. Synapse 57:47–55
127. Kolomeets NS, Orlovskaya DD, Uranova NA (2007) Decreased numerical density of CA3 hippocampal mossy fiber synapses in schizophrenia. Synapse 61:615–621

128. Nowakowski C, Kaufmann WA, Adlassnig C, Maier H, Salimi K, Jellinger KA, Marksteiner J (2002) Reduction of chromogranin B-like immunoreactivity in distinct subregions of the hippocampus from individuals with schizophrenia. Schizophr Res 58:43–53
129. Weickert CS, Rothmond DA, Hyde TM, Kleinman JE, Straub RE (2008) Reduced DTNBP1 (dysbindin-1) mRNA in the hippocampal formation of schizophrenia patients. Schizophr Res 98:105–110
130. O'Tuathaigh CMP, Babovic D, O'Meara G, Clifford JJ, Croke DT, Waddington JL (2007) Susceptibility genes for schizophrenia: characterisation of mutant mouse models at the level of phenotypic behaviour. Neurosci Biobehav Rev 31:60–78
131. Takao K, Toyama K, Nakanishi K, Hattori S, Takamura H, Takeda M, Miyakawa T, Hashimoto R (2008) Impaired long-term memory retention and working memory in sdy mutant mice with a deletion in Dtnbp1, a susceptibility gene for schizophrenia. Mol Brain 1:11
132. Numakawa T, Yagasaki Y, Ishimoto T, Okada T, Suzuki T, Iwata N, Ozaki N, Taguchi T, Tatsumi M, Kamijima K, Straub RE, Weinberger DR, Kunugi H, Hashimoto R (2004) Evidence of novel neuronal functions of dysbindin, a susceptibility gene for schizophrenia. Hum Mol Genet 13:2699–2708
133. Chen X-W, Feng Y-Q, Hao C-J, Guo X-L, He X, Zhou Z-Y, Guo N, Huang H-P, Xiong W, Zheng H, Zuo P-L, Zhang CX, Li W, Zhou Z (2008) DTNBP1, a schizophrenia susceptibility gene, affects kinetics of transmitter release. J Cell Biol 181:791–801
134. Benson MA, Newey SE, Martin-Rendon E, Hawkes R, Blake DJ (2001) Dysbindin, a novel coiled-coil-containing protein that interacts with the dystrobrevins in muscle and brain. J Biol Chem 276:24232–24241
135. Talbot K, Eidem WL, Tinsley CL, Benson MA, Thompson EW, Smith RJ, Hahn C-G, Siegel SJ, Trojanowski JQ, Gur RE, Blake DJ, Arnold SE (2004) Dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampal formation in schizophrenia. J Clin Invest 113:1353–1363
136. Fatemi SH, Earle JA, McMenomy T (2000) Reduction in Reelin immunoreactivity in hippocampus of subjects with schizophrenia, bipolar disorder and major depression. Mol Psychiatry 5:654–663
137. Eastwood SL, Harrison PJ (2006) Cellular basis of reduced cortical reelin expression in schizophrenia. Am J Psychiatry 163:540–542
138. Rioux L, Arnold SE (2005) The expression of retinoic acid receptor alpha is increased in the granule cells of the dentate gyrus in schizophrenia. Psychiatry Res 133:13–21
139. Arnold SE, Talbot K, Hahn C-G (2005) Neurodevelopment, neuroplasticity, and new genes for schizophrenia. Prog Brain Res 147:319–345
140. Kamnasaran D, Muir WJ, Ferguson-Smith MA, Cox DW (2003) Disruption of the neuronal PAS3 gene in a family affected with schizophrenia. J Med Genet 40:325–332
141. Erbel-Sieler C, Dudley C, Zhou Y, Wu X, Estill SJ, Han T, Diaz-Arrastia R, Brunskill EW, Potter SS, McKnight SL (2004) Behavioral and regulatory abnormalities in mice deficient in the NPAS1 and NPAS3 transcription factors. Proc Natl Acad Sci USA 101:13648–13653
142. Pieper AA, Wu X, Han TW, Estill SJ, Dang Q, Wu LC, Reece-Fincanon S, Dudley CA, Richardson JA, Brat DJ, McKnight SL (2005) The neuronal PAS domain protein 3 transcription factor controls FGF-mediated adult hippocampal neurogenesis in mice. Proc Natl Acad Sci USA 102:14052–14057
143. Meyer KD, Morris JA (2008) Immunohistochemical analysis of Disc1 expression in the developing and adult hippocampus. Gene Expr Patterns 8:494–501
144. Austin CP, Ky B, Ma L, Morris JA, Shughrue PJ (2004) Expression of Disrupted-In-Schizophrenia-1, a schizophrenia-associated gene, is prominent in the mouse hippocampus throughout brain development. Neuroscience 124:3–10
145. Miyoshi K, Honda A, Baba K, Taniguchi M, Oono K, Fujita T, Kuroda S, Katayama T, Tohyama M (2003) *Disrupted-In-Schizophrenia 1*, a candidate gene for schizophrenia, participates in neurite outgrowth. Mol Psychiatry 8:685–694
146. Austin CP, Ma L, Ky B, Morris JA, Shughrue PJ (2003) *DISC1* (Disrupted in Schizophrenia-1) is expressed in limbic regions of the primate brain. Neuroreport 14:951–954
147. James R, Adams RR, Christie S, Buchanan SR, Porteous DJ, Millar JK (2004) Disrupted in Schizophrenia 1 (DISC1) is a multicompartmentalized protein that predominantly localizes to mitochondria. Mol Cell Neurosci 26:112–122
148. Duan X, Chang JH, Ge S, Faulkner RL, Kim JY, Kitabatake Y, Liu X-b, Yang C-H, Jordan JD, Ma DK, Liu CY, Ganesan S, Cheng H-J, Ming G-l, Lu B, Song H (2007) Disrupted-In-Schizophrenia 1 regulates integration of newly generated neurons in the adult brain. Cell 130:1146–1158
149. Lauer M, Beckmann H, Senitz D (2003) Increased frequency of dentate granule cells with basal dendrites in the hippocampal formation of schizophrenics. Psychiatry Res 122:89–97
150. Faulkner RL, Jang M-H, Liu X-B, Duan X, Sailor KA, Kim JY, Ge S, Jones EG, Ming G-l, Song H, Cheng H-J (2008) Development of hippocampal mossy fiber synaptic outputs by new neurons in the adult brain. Proc Natl Acad Sci USA 105:14157–14162
151. Kvajo M, McKellar H, Arguello PA, Drew LJ, Moore H, MacDermott AB, Karayiorgou M, Gogos JA (2008) A mutation in mouse *Disc1* that models a schizophrenia risk allele leads to specific alterations in neuronal architecture and cognition. Proc Natl Acad Sci USA 105:7076–7081
152. Contractor A, Swanson G, Heinemann SF (2001) Kainate receptors are involved in short- and long-term plasticity at mossy fiber synapses in the hippocampus. Neuron 29:209–216
153. Breustedt J, Schmitz D (2004) Assessing the role of $GLUK_5$ and $GLUK_6$ at hippocampal mossy fiber synapses. J Neurosci 24:10093–10098
154. Shaltiel G, Maeng S, Malkesman O, Pearson B, Schloesser RJ, Tragon T, Rogawski M, Gasior M, Luckenbaugh D, Chen G, Manji HK (2008) Evidence for the involvement of the kainate receptor subunit GluR6 (GRIK2) in mediating behavioral displays related to behavioral symptoms of mania. Mol Psychiatry 13:858–872
155. Seress L, Mrzljak L (1987) Basal dendrites of granule cells are normal features of the fetal and adult dentate gyrus of both monkey and human hippocampal formations. Brain Res 405:169–174
156. Blaabjerg M, Zimmer J (2007) The dentate mossy fibers: structural organization, development and plasticity. Prog Brain Res 163:85–107
157. Urban NN, Henze DA, Lewis DA, Barrionuevo G (1996) Properties of LTP induction in the CA3 region of the primate hippocampus. Learn Mem 3:86–95
158. St John JL, Rosene DL, Luebke JI (1997) Morphology and electrophysiology of dentate granule cells in the rhesus monkey: comparison with the rat. J Comp Neurol 387:136–147
159. Ariwodola OJ, Crowder TL, Grant KA, Daunais JB, Friedman DP, Weiner JL (2003) Ethanol modulation of excitatory and inhibitory synaptic transmission in rat and monkey dentate granule neurons. Alcohol Clin Exp Res 27:1632–1639
160. Bai O, Chlan-Fourney J, Bowen R, Keegan D, Li X-M (2003) Expression of brain-derived neurotrophic factor mRNA in rat hippocampus after treatment with antipsychotic drugs. J Neurosci Res 71:127–131
161. Barr AM, Young CE, Phillips AG, Honer WG (2006) Selective effects of typical antipsychotic drugs on SNAP-25 and synapto-

physin in the hippocampal trisynaptic pathway. Int J Neuropsychopharmacol 9:457–463
162. Newton SS, Duman RS (2007) Neurogenic actions of atypical antipsychotic drugs and therapeutic implications. CNS Drugs 21:715–725
163. Halim ND, Weickert CS, McClintock BW, Weinberger DR, Lipska BK (2004) Effects of chronic haloperidol and clozapine treatment on neurogenesis in the adult rat hippocampus. Neuropsychopharmacology 29:1063–1069
164. Kodama M, Fujioka T, Duman RS (2004) Chronic olanzapine or fluoxetine administration increases cell proliferation in hippocampus and prefrontal cortex of adult rat. Biol Psychiatry 56:570–580
165. Schmitt A, Weber S, Jatzko A, Braus DF, Henn FA (2004) Hippocampal volume and cell proliferation after acute and chronic clozapine or haloperidol treatment. J Neural Transm 111:91–100
166. Green W, Patil P, Marsden CA, Bennett GW, Wigmore PM (2006) Treatment with olanzapine increases cell proliferation in the subventricular zone and prefrontal cortex. Brain Res 1070:242–245
167. Wakade CG, Mahadik SP, Waller JL, Chiu F-c (2002) Atypical neuroleptics stimulate neurogenesis in adult rat brain. J Neurosci Res 69:72–79
168. Wang H-D, Dunnavant FD, Jarman T, Deutch AY (2004) Effects of antipsychotic drugs on neurogenesis in the forebrain of the adult rat. Neuropsychopharmacology 29:1230–1238
169. Kippin TE, Kapur S, van der Kooy D (2005) Dopamine specifically inhibits forebrain neural stem cell proliferation, suggesting a novel effect of antipsychotic drugs. J Neurosci 25:5815–5823
170. Dawirs RR, Hildebrandt K, Teuchert-Noodt G (1998) Adult treatment with haloperidol increases dentate granule cell proliferation in the gerbil hippocampus. J Neural Transm 105:317–327
171. Möller H-J (2003) Management of the negative symptoms of schizophrenia: new treatment options. CNS Drugs 17:793–823
172. Strange PG (2001) Antipsychotic drugs: importance of dopamine receptors for mechanisms of therapeutic actions and side effects. Pharmacol Rev 53:119–133
173. Hiramoto T, Kanda Y, Satoh Y, Takishima K, Watanabe Y (2007) Dopamine D_2 receptor stimulation promotes the proliferation of neural progenitor cells in adult mouse hippocampus. Neuroreport 18:659–664
174. Yang P, Arnold SA, Habas A, Hetman M, Hagg T (2008) Ciliary neurotrophic factor mediates dopamine D_2 receptor-induced CNS neurogenesis in adult mice. J Neurosci 28:2231–2241
175. Müller N, Schwarz M (2006) Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. Neurotox Res 10:131–148
176. Cartmell J, Monn JA, Schoepp DD (1999) The metabotropic glutamate 2/3 receptor agonists LY354740 and LY379268 selectively attenuate phencyclidine versus *d*-amphetamine motor behaviors in rats. J Pharmacol Exp Ther 291:161–170
177. Patil ST, Zhang L, Martenyi F, Lowe SL, Jackson KA, Andreev BV, Avedisova AS, Bardenstein LM, Gurovich IY, Morozova MA, Mosolov SN, Neznanov NG, Reznik AM, Smulevich AB, Tochilov VA, Johnson BG, Monn JA, Schoepp DD (2007) Activation of mGlu2/3 receptors as a new approach to treat schizophrenia: a randomized Phase 2 clinical trial. Nat Med 13:1102–1107
178. Kamiya H, Shinozaki H, Yamamoto C (1996) Activation of metabotropic glutamate receptor type 2/3 suppresses transmission at rat hippocampal mossy fibre synapses. J Physiol 493:447–455
179. Macek TA, Winder DG, Gereau RW IV, Ladd CO, Conn PJ (1996) Differential involvement of group II and group III mGluRs as autoreceptors at lateral and medial perforant path synapses. J Neurophysiol 76:3798–3806
180. Olincy A, Stevens KE (2007) Treating schizophrenia symptoms with an alpha7 nicotinic agonist, from mice to men. Biochem Pharmacol 74:1192–1201
181. Freedman R, Olincy A, Buchanan RW, Harris JG, Gold JM, Johnson L, Allensworth D, Guzman-Bonilla A, Clement B, Ball MP, Kutnick J, Pender V, Martin LF, Stevens KE, Wagner BD, Zerbe GO, Soti F, Kem WR (2008) Initial phase 2 trial of a nicotinic agonist in schizophrenia. Am J Psychiatry 165:1040–1047
182. Leonard S, Freedman R (2006) Genetics of chromosome 15q13-q14 in schizophrenia. Biol Psychiatry 60:115–122
183. Breese CR, Adams C, Logel J, Drebing C, Rollins Y, Barnhart M, Sullivan B, Demasters BK, Freedman R, Leonard S (1997) Comparison of the regional expression of nicotinic acetylcholine receptor α7 mRNA and [^{125}I]- α-bungarotoxin binding in human postmortem brain. J Comp Neurol 387:385–398
184. Young JW, Crawford N, Kelly JS, Kerr LE, Marston HM, Spratt C, Finlayson K, Sharkey J (2007) Impaired attention is central to the cognitive deficits observed in alpha 7 deficient mice. Eur Neuropsychopharmacol 17:145–155
185. Fernandes C, Hoyle E, Dempster E, Schalkwyk LC, Collier DA (2006) Performance deficit of α7 nicotinic receptor knockout mice in a delayed matching-to-place task suggests a mild impairment of working/episodic-like memory. Genes Brain Behav 5:433–440
186. Gray R, Rajan AS, Radcliffe KA, Yakehiro M, Dani JA (1996) Hippocampal synaptic transmission enhanced by low concentrations of nicotine. Nature 383:713–716
187. Sharma G, Vijayaraghavan S (2003) Modulation of presynaptic store calcium induces release of glutamate and postsynaptic firing. Neuron 38:929–939
188. Sharma G, Grybko M, Vijayaraghavan S (2008) Action potential-independent and nicotinic receptor-mediated concerted release of multiple quanta at hippocampal CA3-mossy fiber synapses. J Neurosci 28:2563–2575
189. Vogt KE, Regehr WG (2001) Cholinergic modulation of excitatory synaptic transmission in the CA3 area of the hippocampus. J Neurosci 21:75–83
190. van Neerven S, Kampmann E, Mey J (2008) RAR/RXR and PPAR/RXR signaling in neurological and psychiatric diseases. Prog Neurobiol 85:433–451
191. Webster MJ, Knable MB, O'Grady J, Orthmann J, Weickert CS (2002) Regional specificity of brain glucocorticoid receptor mRNA alterations in subjects with schizophrenia and mood disorders. Mol Psychiatry 7:985–994
192. Perlman WR, Tomaskovic-Crook E, Montague DM, Webster MJ, Rubinow DR, Kleinman JE, Weickert CS (2005) Alteration in estrogen receptor α mRNA levels in frontal cortex and hippocampus of patients with major mental illness. Biol Psychiatry 58:812–824
193. Barbeau D, Liang JJ, Robitalille Y, Quirion R, Srivastava LK (1995) Decreased expression of the embryonic form of the neural cell adhesion molecule in schizophrenic brains. Proc Natl Acad Sci USA 92:2785–2789
194. Dean B, Opeskin K, Pavey G, Hill C, Keks N (1997) Changes in protein kinase C and adenylate cyclase in the temporal lobe from subjects with schizophrenia. J Neural Transm 104:1371–1381
195. Tian SY, Wang J-F, Bezchlibnyk YB, Young LT (2007) Immunoreactivity of 43 kDa growth-associated protein is decreased in post mortem hippocampus of bipolar disorder and schizophrenia. Neurosci Lett 411:123–127
196. Goldsmith SK, Joyce JN (1995) Alterations in hippocampal mossy fiber pathway in schizophrenia and Alzheimer's disease. Biol Psychiatry 37:122–126