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Psychosis and Adhesion Molecules

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1. Introduction

Schizophrenia is a chronic, severe, and disabling brain disorder that affects about 1% of the population worldwide. However the etiology and pathophysiology is poorly understood. It has been determined that schizophrenia is a multifactorial disorder influenced by genetic, neurodevelopmental and social factors (Mueser & McGurk, 2004; Weinberger, 1987). Numbers of linkage and association studies have shown that multiple susceptibility genes such as DISC1, Neureglin1, DTNBP1, RGS4, G72 were involved in the development of schizophrenia (Sibylle *et al*., 2009). Moreover, accumulating evidence from recent studies suggests that environmental risk factors during fetal and perinatal life also contribute to the development of schizophrenia. The environmental risk factors of schizophrenia have been reported, such as infections, nutritional deficiencies, paternal age, fetal/neonatal hypoxic and obstetric insults and complications and maternal stress and other exposures (Brown AS, 2011). Postmortem human brain and developmental animal model of schizophrenia studies have shown abnormal neurodevelopment at sequential stages of brain development. Initial postmortem studies appeared to support the early neurodevelopmental model in neuronal migration and organization, considered fetal in origin (Jakob et al, 1986; Akbarian et al, 1993). Subsequent and more reproducible observations of reduced neuronal size and arborization, which could have developed later in life, indicated that the pathophysiological processed involved in schizophrenia need not be restricted to the pre- or perinatal period (Selemon et al, 1999). Candidate genes for schizophrenia are typically expressed across developmental periods, often in different brain regions.

Adhesion molecules are membrane-anchored molecules whose extracellular domains directly interact to help hold the membranes of two cells together. Adhesion might be a primary role of the interaction or it could be an epiphenomenon of ligand-receptor signals to the cell interior. The major families of adhesion molecules are cadherins, immunoglobulin superfamilies and integrins. Cadherins constitute a superfamily that is comprised of more than 100 members in vertebrates, grouped into subfamilies that are designated as classic cadherins, desmosomal cadherins, protocadherins, Flamingo/ CELSRs and FAT (Takeichi, 2006). Cadherins are calcium dependent, singlepass transmembrane molecules with five ectodomain repeats, which mediate mainly homophilic (more rarely heterophilic) adhesion

(Tepass *et al*, 2000). Strong cadherin adhesion is believed to be dependent on the formation of *cis* which the bind in *trans* to form adhesive `zippers` (Shan *et al*, 2000). The cytoplasmic domains of the cadherins contain binding sites for the catenins, which provide links to the cytoskeleton and mediate signaling (Yap *et al*, 2003). N-cadherin was one of the first adhesion molecules shown to be concentrated in the synaptic cleft (Yamagata et al, 1995), a localization subsequently shown for catenins and several other cadherins at several synaptic types. Immunogloblin superfamily molecules contain varying numbers of extracellular cysteine-looped domains first described in immunogloblins. Many have one or more fibronectin type III (FNIII) repeats between the immunoglobulin domains and the membrane (Rougon and Hobert, 2003). The integrin family of cell surface receptors is a major mediator of cell-cell and cell-extracellula matrix (ECM) interactions. Integrins can efficiently transducer signals to and from the external cell environment to the intracellular signaling and cytoskeletal compartments, while modulating signaling cascades initiated by other cellular receptors. Functional integrin receptors are formed by membrane spanning heterodimers of α and β subunits. There are at least 18 α and 8 β subunits that can form more than 20 different integrin receptors.

Major depressive disorder (MDD) is one of the mood disorders associated with significant morbidity. MDD is thought to be a multifactorial disease related to both environmental and genetic factors, though the genes responsible and the pathogenesis of major depression at the molecular level remain unclear. Among many environmental factors, repeated stressful events are associated with the onset of depression, and stress activates the hypothalamic–pituitary–adrenocortical (HPA) system (Gold et al., 1988a, b; Post, 1992; Bartanusz et al., 1993; Herman et al., 1995; Aguilera and Rabadan-Diehl, 2000; McEwen, 2004; Sala et al., 2004; Alfonso et al., 2005; Dallman et al., 2006). The negative feedback of corticosteroids on the HPA system occurs at the level of the hypothalamus and the anterior pituitary via the glucocorticoid receptors (Thomson and Craighead, 2008; Pariante and Lightman, 2008).

Dysregulation of this negative feedback mechanism is reported in patients with major depressive disease, which results in hyperactivity of the HPA system and higher basal levels of serum corticosterone (Carroll et al., 1976; Holsboer et al., 1984; Nemeroff et al., 1984; Halbreich et al., 1985a, b; Schatzberg et al., 1985; Gold et al., 1986a; Young et al., 1993). In addition, many clinical cases demonstrate that elevated corticosterone levels trigger depressive symptoms (Schatzberg et al., 1985; Gold et al., 1986b; Chu et al., 2001). These facts strongly indicate that sustained elevated levels of plasma corticosteroids are one of the causes of major depressive diseases.

Recent we showed that chronically elevated plasma corticosterone levels by exposing mice to repeated stress induced the upregulation of adhesion molecules such as N-cadherin, α-catenin, and β-catenin in the oligodendrocytes via the activation of phosphatidylinositol 3-kinase (PI3K)–3-phosphoinositide-dependent protein kinase (PDK1)–serum/glucocorticoid regulated kinase (SGK1)–N-myc downstream-regulated gene 1 (NDRG1) pathway, resulting in morphological changes in the oligodendrocytes (OLs) (Miyata et al., 2011). These findings show that SGK1 changes adhesion molecules expression levels and regulates the plasticity of the processes of the OLs under the stressful condition.

It has been known that adhesion molecules such as cadherins and integrins played important roles in neuronal development and function. Furthermore, in recent years, genetic association studies have been supporting the involvement of adhesion molecules in

psychosis such as schizophrenia, bipolar disorder and autism. In this chapter, we will focus on the role of adhesion molecules in psychiatric disorders, especially schizophrenia and depression.

2. Schizophrenia and adhesion molecules

2.1 The major mental disorders related adhesion molecules

The major mental disorders such as schizophrenia, bipolar disorder and autism are substantially influenced by genetic factors. Recent genomic studies have identified a small number of common and rare risk genes contributing to these disorders and support epidemiological evidence that genetic susceptibility overlaps in these disorders (Lichtenstein *et al*, 2009). To date, a number of genetic association analyses have shown that genes coding adhesion molecules associated with schizophrenia, bipolar disorder and autism. A molecular pathway analysis applied to the 212 experimentally-derived pathways in the Kyoto encyclopedia of Genes and Genomics (KEGG) database identified significant association between the cell adhesion molecule (CAM) pathway and both schizophrenia and bipolar disorder susceptibility across three GWAS datasets (O'Dushlaine *et al*, 2011). Interestingly, a similar approach applied to an autistic spectrum disorders (ASDs) sample identified a similar pathway (Wang *et al*, 2009). Disruption of the NRXN1 gene has been reported in both schizophrenia and autism cases or families (Walsh *et al*, 2008; Szatmari *et al*, 2007). Axonal neurexins form trans-membrane complexes with neuroligin on dendrites and are required for the formation of synaptic contacts and for efficient neurotransmission-including maintaining postsynaptic NMDA receptor function. CDH4 is a classical cadherin thought to be involved in brain segmentation and neurite outgrowth. Total cerebral brain volume was the only genome-wide significant finding to emerge from a GWAS study of brain aging using MRI and cognitive assessment of 705 healthy participants from the Framingham study. Reduced brain volumes are a recognized feature of schizophrenia and this may point to a role in maintenance rather than formation of neuronal connections (Seshadri *et al*, 2007). A recent GWAS study in bipolar disorder and subsequent replication efforts have provided some support for association with CDH7 (Soronen *et al*, 2010). Another GWAS study in autistic spectrum disorders (ASDs) identified association with the chromosome 5q14.1 region containing other members of the cadherin superfamily, CDH9 and CDH10 (Wang et al, 2009). A number of microdeletion/microduplication syndromes have been identified that are associated with schizophrenia, ASDs, intellectual disability, specific language delay and other neurodevelopmental phenotypes. Many of these disrupt genes involved in CAM pathways. For instance, disruption of NRXN1 has been reported in cases of both autism and schizophrenia. CASK deletions are reported in individual with learning disability and brain malformation phenotypes. Disruption of CNTNAP1 has been reported in autism, language disorder and schizophrenia. A deletion between two cadherin (CDH12 and CDH18) genes on 5p14 was identified in a monozygotic twin pair discordant for schizophrenia. This 11kb deletion is present in the affected but not in the unaffected twin. Taken together, it is possible that susceptibility to schizophrenia, bipolar disorder and ASDs may involve common molecular aetiology where an accumulation of small effects from many common genetic risk variants or more highly penetrant mutations induce neuronal dysconnectivity by disrupting adhesion molecule function.

2.2 Involvement of N-cadherin and β1-integrin in neuronal development

Neural development and the organization of complex neuronal circuits involve a number of processed that require cell-cell and cell-matrix interaction. Vertebrate N-cadherin is expressed from the beginning of neural development, and its expression persists in differentiated neurons in various species (Hatta & Takeichi, 1986). Conventional knockout of the mouse N-cadherin gene causes early embryonic lethality, mainly because of heart defects (Radice *et al*, 1997). Therefore, the precise roles of N-cadherin in neuronal development at later developmental stages remain less clear. Nevertheless, some fragmental information on the specific role of N-cadherin in axon projection is available: studies using blocking antibodies against N-cadherin showed that this molecule is required for the correct innervations of specific laminae in the chicken tectum by retinal optic nerves (Inoue & Sanes, 1997). Some of the type II cadherins are involved in axon sorting and in the regulation of physiological function of the brain, such as long-term potentiation in the hippocampus. When a dominant-negative N-cadherin of which extracellular domain was deleted was expressed in the neural retina of *Xenopus* embryos, the extension of neurites from retinal ganglion cells was inhibited. Such N-cadherin mutant form was able to block the radial extension of horizontal cell dendrites, as well as their synaptic connections with photoreceptor cells in the retina. Furthermore, the mutant forms were used to show that cadherins are required for tangential migration of precerebellar neurons (Taniguchi et al, 2006). These results provide evidence that N-cadherin has important roles in neural cell-cell interactions and neurite extension in various systems.

As in the case of N-cadherin, β1-integrin also expresses at early developmental stage of the nervous system. Neural crest cells express many integrins and migrate through an extracellular matrix (ECM)-rich environment (Bronner-Fraser, 1994). In mice, genetic ablation of β1-integrin results in severe perturbations of the peripheral nervous system, including failure of normal nerve arborization, delay in Schwann cell migration, and defective neuromuscular junction differentiation, In addition to direct effects on migration, it has been shown that absence of specific integrin heterodimers compromises Schwann cell precursor survival, proliferation and differentiation (Pietri *et al*, 2004). Many of these observations are likely to reflect the roles of integrin receptors in regulating activation of MAP kinase, Rac, and other signaling pathways. In central nervous system, integrin deletion affects many aspects of forebrain and cerebellar development. Loss of β1-integrin results in disruptions of the basal lamina that separates the brain from the overlying mesenchyme. As a result, the migration of neurons is perturbed, resulting in abnormal lamination of the cortex and cerebellum. Although some evidence indicates that integrins modeulate neuronal interactions with radial glia which provide the substrate for the tangential migrations that establish the cortical lamination pattern (Sanada et al, 2004; Schmid et al, 2005), the major phenotype observed in β1-integrin defect models appears to stem form disruption of signaling pathways controlling neuronal migration that require integrity of the basal lamina. Although Localization studies indicate that integrins are present at synapses in the brain, genetic and pharmacological studies indicate that integrins are not required for synapse formation, but are required for normal synaptic plasticity. The presence of integrins in the mushroom body of the *Drosophila* brain was shown to be required for short-term memory. Studies in the murine hippocampus have demonstrated that β1-integrin were required for normal LTP (Chan *et al*, 2006; Huang *et al*, 2006)). Studies of mice with reduced expression of individual β1-integrin heterodimers have suggested that specific integrins have different

functions at the synapse indicate that integrins are involved in regulation of both NMDA and AMPA receptor function and act through regulation of protein kinases and the actin cytoskeleton.

2.2.1 DISC1 is involved in neuronal development

Disrupted-in-schizophrenia 1 (DISC1) is a promising candidate susceptibility gene for major mental disorders, including schizophrenia. *DISC1* was originally identified at the break point of a balanced (1;11) (q42.1;q14.3) translocation that segregates with major mental illnesses in a large Scottish family (Millar *et al*, 2001). Recent linkage and association studies demonstrated association between DISC1 and schizophrenia in multiple populations, suggesting that DISC1 is a general risk factor for schizophrenia (Jaaro-Peled *et al*, 2009; Chubb *et al*, 2008; Hodgkinson *et al*, 2004; Cannon *et al*, 2005). To investigate the physiological roles of DISC1, a number of groups, including ours, have identified DISC1-interacting proteins, such as the fasciculation and elongation protein zeta-1 (FEZ1) (Miyoshi *et al*, 2003), DISC1-binding zinc-finger protein (DBZ) (Hattori *et al*, 2007), kendrin (Miyoshi *et al*, 2004), NudE-like (NDEL1/NUDEL) protein (Ozeki *et al*, 2003; Morris *et al*, 2003) and BBS1 (Ishizuka et al, 2011). Other relevant interacting proteins include GSK3b and PDE4B (Millar *et al*, 2005), which are involved in intracellular signaling pathways. The endogenous expression pattern of DISC1 is complex, and DISC1 co-localizes with centrosomal protein, mitochondria, and F-actin. DISC1 protein has conserved nuclear localization signals and has been found within the nuclei of certain cell types. Moreover, DISC1 is involved in cAMP, CREB, Notch, Wnt and MAPK signaling pathways. Recent studies have suggested that DISC1 plays various roles in cell proliferation, neural migration, dendritic development and synapse maintenance during neurodevelopment and influences adult brain functions.

2.2.2 DISC1 regulates N-cadherin expression

The strength of cell-cell adhesion is associated with the expression levels of cadherins at the cell surface (Steinberg & Takeichi, 1994). In neural cells, neural cell adhesion molecule (NCAM) and N-cadherin are two of the major adhesion molecules (Kiryushko *et al*, 2004). We have demonstrated that DISC1 induced cell adhesion through an increase in N-cadherin expression in PC12 cells (Fig. 1.a.c.d). Furthermore, the increased N-cadherin was concentrated at the cell-cell contact zone, showing that increased N-cadherin functions at cell-cell contact sites (Fig. 1.b). Our real-time PCR analysis showed up-regulation and down-regulation of N-cadherin mRNAs by DISC1 overexpression and knock-down in PC12 cells, respectively. Furthermore, the down-regulation of N-cadherin protein expression (at 72 hours after transfection) by DISC1 siRNA followed that of N-cadherin mRNA expression (at 48 hours after transfection). The expression levels of N-cadherin protein in DISC1-overexpressing cells were correlated with those of mRNA. The results using NLS1-deleted DISC1 (DISC1(46–854)-GFP) indicates that the expression of N-cadherin was regulated by nuclear DISC1. It is possible that nuclear DISC1 regulates level of N-cadherin mRNA , because a role for nuclear DISC1 in association with gene transcription was reported (Ma *et al*, 2002). Moreover, immunoprecipitation assays show that DISC1 does not interact with either N-cadherin suggesting that DISC1 does not regulate the expression of these molecules directly. In hippocampal neurons, DISC1 also enhanced N-cadherin, which accumulated at cell-cell contact sites, suggesting that the enhanced N-cadherin also functions at cell surfaces of neurons (Fig. 3.).

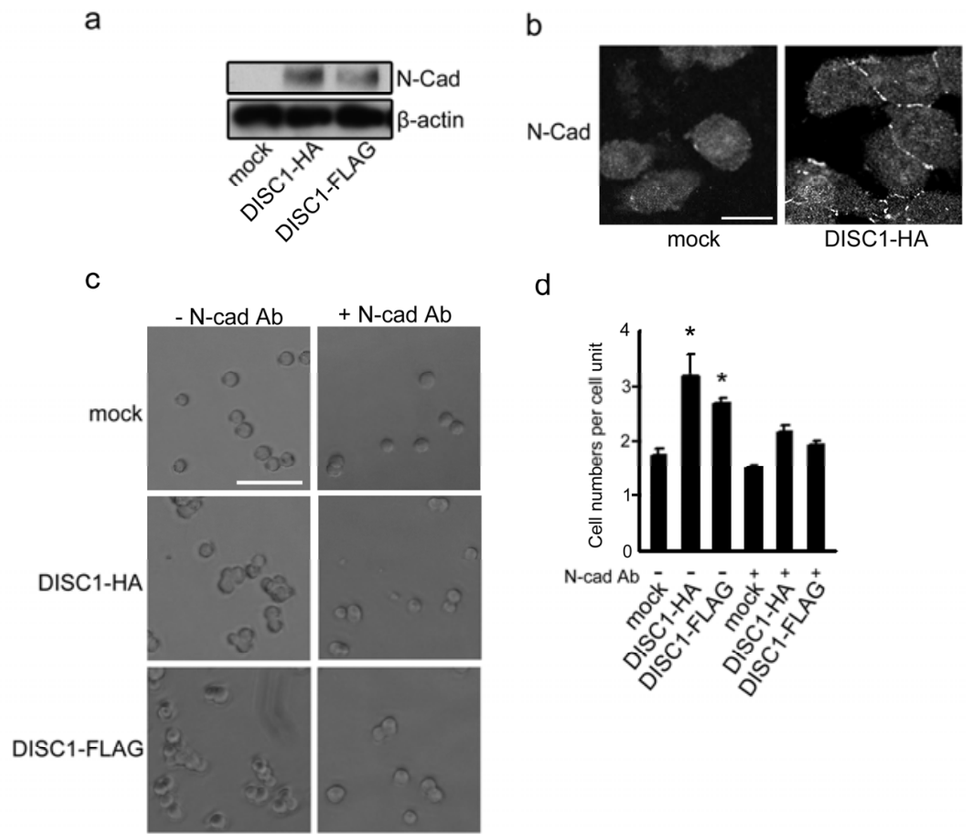


Fig. 1. DISC1 enhances cell-cell adhesion via increasing the expression level of N-cadherin. (a) Effect of DISC1 on the level of N-cadherin. PC12/mock, PC12/DISC1-HA and PC12/DISC1-FLAG stable cells were lysed and subjected to western blot analysis. (b) PC12/mock and PC12/DISC1-HA cells were fixed and immunostained with anti-N-cadherin antibody. (c) PC12 cells were dissociated with trypsin-EDTA and cultured on collagen-coated dishes for 2 hours in the presence of anti-N-cadherin antibody or rabbit IgG. Phase-contrast images are shown. Scale bar, 100 μm. (d) To quantify the results in (c), the average number of cells per unit, which consisted of a single cell or a cluster of two or more cells, was determined. Over 100 cells were examined in each case. Values are the means±s.e.m. of at least three independent experiments. *p<0.05 vs mock in the absence of anti-N-cadherin (Student's t-test).

2.2.3 DISC1 regulates β1-integrin expression

PC12 cells provide an excellent experimental system for studying the mechanisms of neurite outgrowth. It has been reported that DISC1 enhances neurite outgrowth of PC12 cells in the presence of nerve growth factor (NGF) (Miyoshi *et al*, 2003; Ozeki *et al*, 2003; Bozyczko *et al*, 1986). Neurite outgrowth of neuronal cells is directly mediated by integrin-ECM interactions in developing nervous systems, as well as in a PC12 neurite genesis model (Reichardt & Tomaselli, 1991; Tomaselli *et al*, 1987; Tomaselli *et al*, 1990). We have demonstrated that upregulation of β1-integrin expression by DISC1 enhanced neurite outgrowth by regulating cell-matrix adhesion in PC12 cells (Fig. 2.). This finding is based on the followting results (1) DISC1 overexpression enhanced NGF induced-neurite outgrowth (Fig. 2.b.c). (2) DISC1

overexpression increased β1-integrin expression, especially in the presence of NGF (Fig. 2.a). (3) Inhibition of β1-integrin with anti-β1-integrin antibody suppressed the enhanced neurite outgrowth induced by DISC1 to the control level (Fig. 2.b.c). (4) overexpression of β1-integrin rescued the suppressed neurite outgrowth of DISC1-knockdown cells. (5) DISC1 overexpression enhanced cell-matrix adhesion. The increased expression of β1-integrin by NGF and DISC1 was localized at the cell surface and growth cones of neurites, showting that upregulated β1-integrin at the cell membrane and growth cones of differentiating PC12 cells participates in neurite extension. In support of this idea, integrins, including β1-integrin, have been shown to mediate the promotion of neurite outgrowth. Unlike

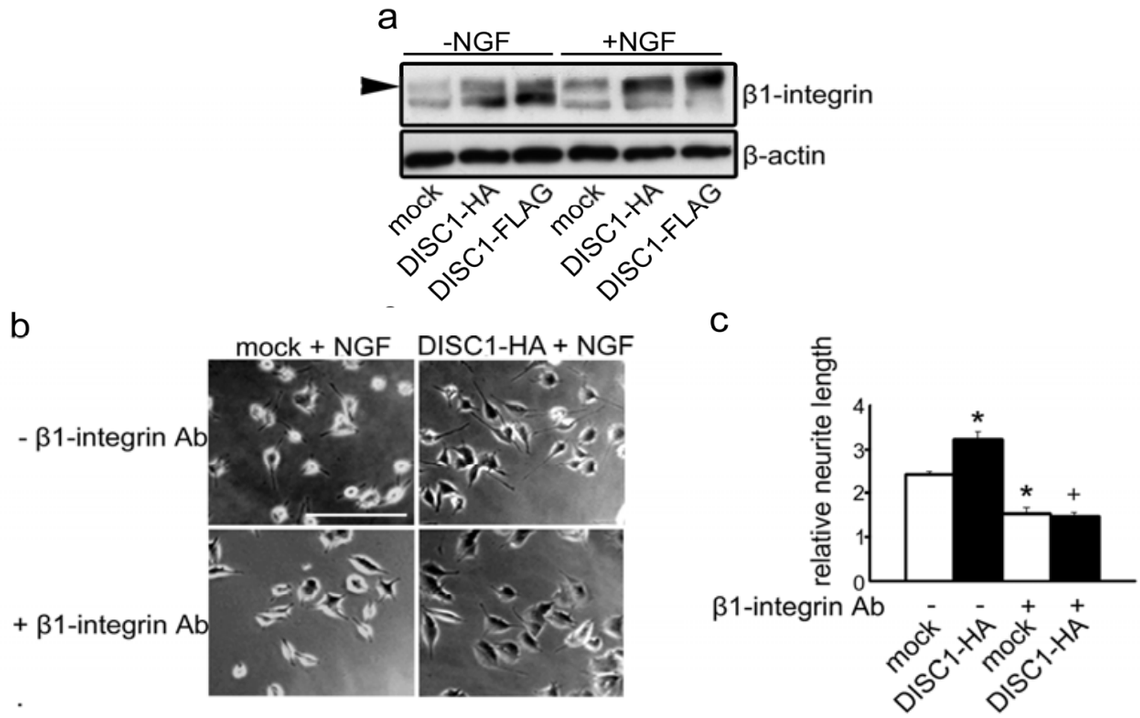


Fig. 2. DISC1 enhances neurite outgrowth via regulating the expression of β1-integrin. (a) Effect of DISC1 on the level of β1-integrin expression in the absence or presence of NGF. PC12/mock, PC12/DISC1-HA or PC12/DISC1-FLAG cells with or without NGF for 24 hours were lysed and subjected to western blot analysis. The arrow indicates the band containing full-length β1-integrin. (a, b) PC12/mock or PC12/DISC1-HA cells treated with anti-β1-integrin antibody were cultured in the presence of NGF for 24 hours. Shown are phase-contrast images of the cells. The left panels show the results for PC12/mock cells with NGF and the right panels results for PC12/DISC1-HA cells with NGF. The upper panels present findings for cells not treated with anti-β1-integrin antibody and the lower panels show findings for cells treated with anti-β1-integrin antibody. Scale bar, 200μm. (c) Quantification of neurite lengths. The neurite length was analyzed on randomly selected digital microscope images. Data are expressed as the means±s.e.m. of at least three independent experiments. At least 100 cells were counted in each case and analyzed in a blinded manner. *$p < 0.05$ vs. mock withoutβ1-integrin antibody, $^{+}p < 0.05$ vs. DISC1-HA without β1-integrin antibody (Student's *t*-test).

N- cadherin, the regulation of β1-integrin expression by DISC1 is not transcriptional. The results using NLS1-deleted DISC1 indicate that the expression of β1-integrin was not regulated by nuclear DISC1. In hippocampal neurons, DISC1 also enhanced the expression of β1-integrin protein at the cell membrane of cell bodies and neurites (Fig. 3.). Therefore, it is possible that upregulation of β1-integrin expression by DISC1 enhances neurite outgrowth by regulating cell-matrix adhesion in primary neurons.

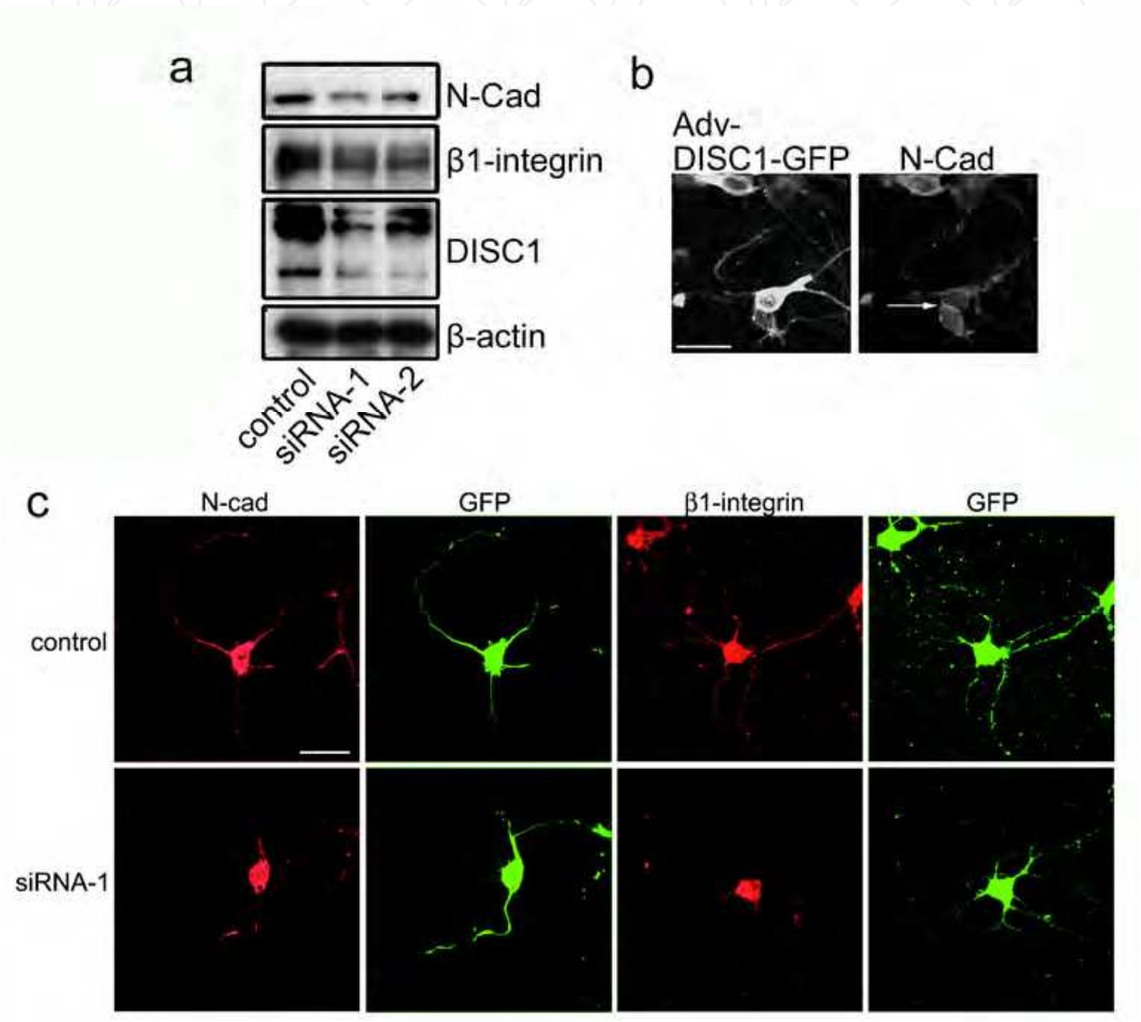


Fig. 3. (a) siRNAs targeting specific DISC1 sequences (siRNA-1 and siRNA-2) or scramble siRNA (control) was transfected into rat primary neurons at 1 DIV and cells were harvested at 4 DIV. The expression of DISC1, N-cadherin and β1-integrin was assayed by western blotting. (b) Adv-DISC1-GFP-infected neurons (1DIV) were fixed (4DIV) and immunostained with anti-N-cadherin. Arrow indicates enhanced N-cadherin expression at cell-cell contact. (c) Scramble or siRNA-1 with GFP-expressing vector-transfected neurons (1 DIV) were fixed (4 DIV) and immunostained with anti-N-cadherin or anti-β1-integrin antibody. Scale bars, 20 μm.

3. Depression and adhesion molecules

Repeated stressful events are known to be closely associated with the onset of depression (Gold et al., 1988a, b; Post, 1992; McEwen, 2004; Sala et al., 2004; Alfonso et al., 2005). Furthermore, chronic stress activates the HPA system chronically by elevation of plasma corticosterone levels (Bartanusz et al., 1993; Herman et al., 1995; Aguilera and Rabadan-Diehl, 2000; Dallman et al., 2006). However, the molecular pathway in the brain caused by the excess level of plasma corticosteroids is hardly elucidated. Here we will show that chronically stressed mice indicates depression-like symptoms and the functional implications of changes in adhesion molecules in the mice brain exposed to chronic stresses.

3.1 Repeated WIRS exposed mice are suitable model of depression-like symptoms

The HPA system is initiated by the activation of the paraventricular nucleus (PVN) of the hypothalamus, leading to the secretion of corticotropin-releasing hormone (CRH) from the neuron terminals of the PVN neurons. CRH triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH subsequently stimulates the release of cortisol or corticosterone in humans and rodents, respectively (Thomson and Craighead, 2008; Pariante and Lightman, 2008). However, the molecular pathway in the brain affected by excess levels of plasma corticosteroids is not known. We firstly established a suitable model of depression-like symptoms wherein the HPA system plays an important role.

The mice exposed to repeated water-immersion restraint stress (WIRS) (chronic stress exposure) demonstrated chronically elevated plasma corticosterone levels. Furthermore, these chronic stress exposed mice showed significant longer immobility times than control mice, indicating increased despair. In addition, exposing mice to chronic stress resulted in a significant decrease in neurogenesis in the hippocampus (Miyata et al., 2011). As demonstrated in the mice exposed to chronic stress, continuous upregulation of plasma corticosterone levels, increased immobility time, and neurogenesis inhibition in the hippocampus are well known to occur in patients with depression.

3.2 Elevation of SGK1 and phosphorylated SGK1 in the OLs after chronic stress exposure

The microarray technique was showed that *Sgk1* consistently altered expression in the medial prefrontal cortex of chronically stressed mice. Furthermore, we recently reported the first *in vivo* and *in vitro* demonstration of chronic stress increases SGK1 expression and SGK1 activation (Miyata et al., 2011). It was previously reported that subcutaneous injection of corticosterone causes the upregulation of SGK1 in OLs (van Gemert et al., 2006), suggesting that various stressors that induce increases in plasma corticosterone levels possibly upregulate SGK1 expression in OLs. Although mechanism that up-regulated corticosterone regulates Sgk1 expression is still obscure (Webster et al., 1993a, b), it is probable that up-regulated corticosterone binds to Sgk1 gene directly to elevate its expression in the OLs, because glucocorticoide responsible element is present at the promoter region of *Sgk1* gene (Maiyar et al., 1996, 1997).

The first step of the activation of SGK1 is phosphorylation at Ser422 by mTOR and other protein kinase (Feng et al., 2004; Hong et al., 2008). The form of posphorylation of SGK1 Ser422 is substrate for the PDK1 which phosphorylates SGK1 at Thr256 in the SGK1 activation loop to cause the activation of SGK1 (Kobayashi et al., 1999; Biondi et al., 2001). In fact, chronic stress exposure resulted in an increase of phosphorylated SGK1 at Thr256 in OLs (Miyata et al., 2011).

3.3 Activated SGK1 up-regulates the expression of the adhesion molecules in OLs *via* elevation of the NDRG1 phosphorylation after chronic stress exposure

Several molecules interacting with Sgk1 in the brain are reported. For example, they are NDRG1, NDRG2, Tau, Huntingtin, IκB kinase α (IKKα) and p300 (Murray et al., 2004; Rungone et al., 2004; Chun et al., 2004; Tai et al., 2009). Among them, NDRG1 has been shown to be localized in OLs in the brain (Okuda et al., 2008) and NDRG1 has shown as the substrate of SGK1 (Murray et al., 2004). The SGK1 and NDRG1 interact in OLs and chronic stress increased both SGK1 and NDRG1 phosphorylation levels (Fig. 4.). We reported that chronic stress elevates the expression of SGK1 and increased SGK1 is phosphorylated SGK1 by the activated PDK1 via PI3K signal pathway (Miyata et al., 2011). However, molecular

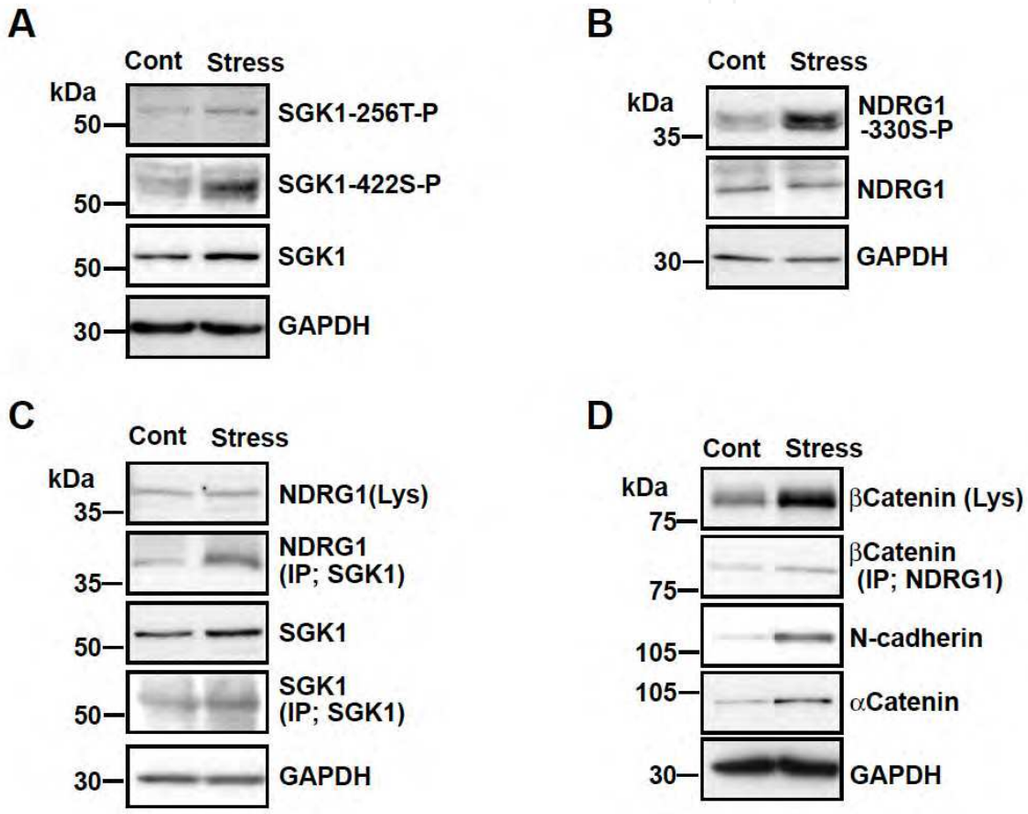


Fig. 4. Activated SGK1-NDRG1 pathway by repeated exposure to WIRS (chronic stress exposure) upregulates adhesion molecules expression levels in oligodendrocytes.
(A) Western blot analysis shows SGK1 protein, its phosphorylation at positions T-256 (SGK1-256T-P) and S-422 (SGK1-422S-P) in the oligodendrocytes of the corpus callosum after chronic stress exposure. (B) Western blot analysis shows that repeated exposure to WIRS elevated phosphorylated NDRG1 levels in the corpus callosum. (C) Immunoprecipitation and western blot analysis show that chronic stress exposure elevated the interaction between SGK1 and NDRG1 (second column). However, NDRG1 expression did not increase in the corpus callosum (first column). (D) Immunoprecipitation and western blot analysis show that repeated exposure to WIRS elevated the interaction between NDRG1 and β-catenin (second panel), and that the expression levels of β-catenin, N-cadherin, and α-catenin were elevated in the corpus callosum. (Adapted with permission from Miyata et al. 2011.)

mechanism of the activation of PI3K signal pathway by enhanced plasma corticosterone level after chronic stress exposure remains unknown.
Recently, NDRG1 has been shown to play a key roll in stabilizing the adherens junctions by up-regulation of recycle of E-cadherin in the prostate cancer cells (Kachhap et al., 2007; Song et al., 2010). We further reported that expression of adhesion molecules such as N-cadherin, α-catenin and β-catenin was increased in the corpus callosum after chronic stress exposure and interaction between NDRG1 and β-catenin (Fig. 4.).

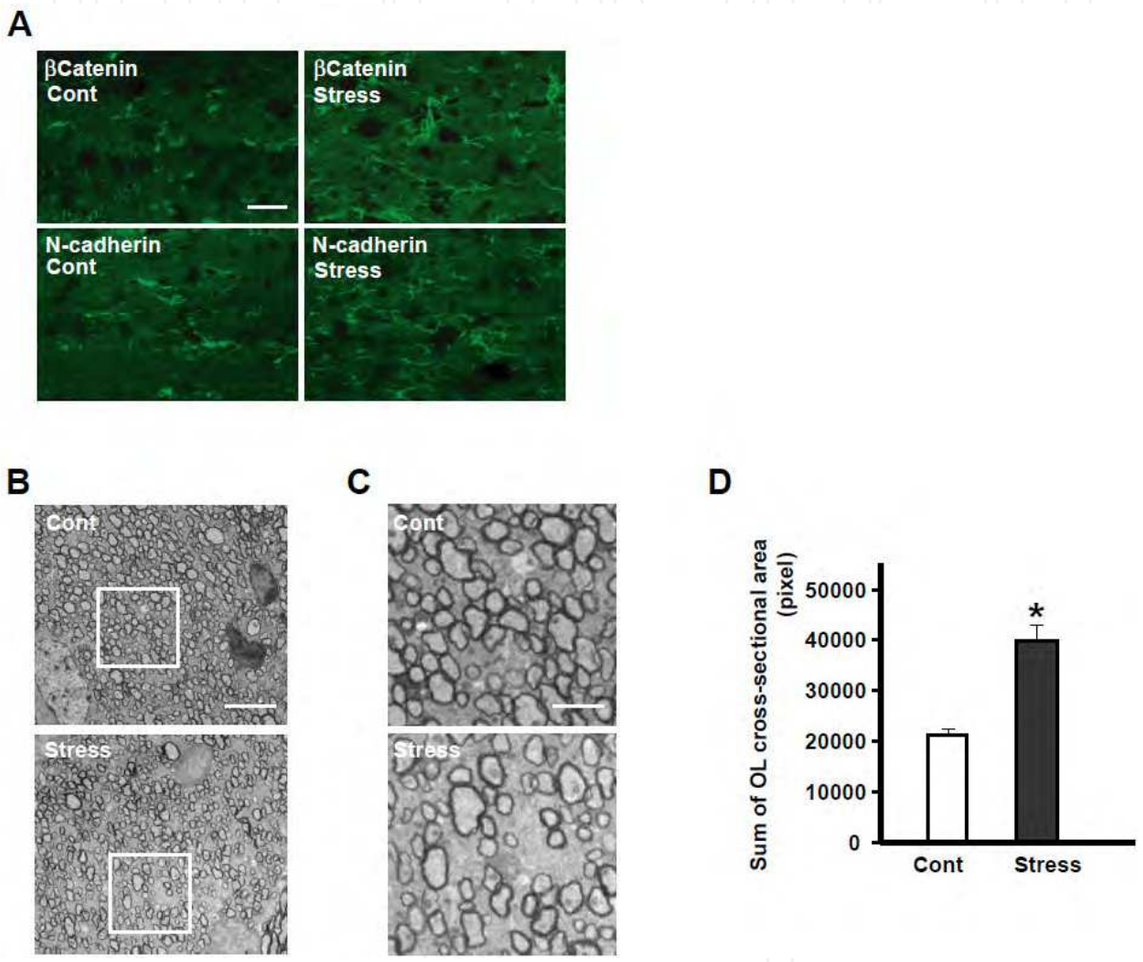


Fig. 5. Chronic stress exposure causes morphological alterations in OLs.
(A) Immunohistochemical analysis of β-catenin and N-cadherin in the corpus callosum demonstrates increased labeling of the processes of the oligodendrocytes (i.e., greater number and intensity) in mice exposed to repeated WIRS. Scale bar = 50 μm. (B, C) Representative transverse electron micrographs of the corpus callosum from control (upper panels of B and C) and chronic stress exposed mice (lower panels of B and C). Scale bars = 5 μm. (E) The higher magnification of the square region of (D). Scale bar = 2 μm. (F) Results of the quantification of the sum of oligodendrocytes in the cross-sectional area. The results are expressed as the mean ± SEM of 3 independent experiments. *$p < 0.05$, t-test. (Adapted with permission from Miyata et al. 2011.)

3.4 Up-regulation of the adhesion molecules expression in OLs causes the morphological changes of OLs and MDD

Adhesion molecules such as N-cadherin, α-catenin and β-catenin are key molecules composing the adherent junction (Aberle et al., 1996). Therefore, increase of the expression of these molecules suggests the extension of the site where OLs are adjacent to other elements. Cellular membrane of OLs and their processes labeled by the N-cadherin and β-catenin after chronic stress exposure increased markedly, showing that chronic stress exposure induces the morphological change of OLs (Fig. 5.). The volume of OL processes occupying the intrafibrial space increased markedly in the corpus callosum of the chronic stress exposure mice comparing with that found in the normal mice (Fig. 5.). Furthermore, the abnormal arborization of OLs and depression-like symptoms returned to the control levels after mice recovered from the chronic stress (Miyata et al., 2011).

4. Conclusion

To date, genetic association studies have been showing that adhesion molecules such as cadherins strongly associated with the development of psychosis including schizophrenia, bipolar disorder and autism, because these disorders have common abnormalities in molecular pathways. Adhesion molecules play important roles in neurodevelopmental events such as neuronal migration, neurite extension, syanptogenesis and synaptic plasticity from early embryo to postnatal stages. Furthermore, we clarified that DISC1, a candidate susceptibility gene for major mental illness, regulates the expressions of adhesion molecules, which affect cellular adhesion and neurite outgrowth. Taken together these results, abnormality of adhesion molecules caused by genetic susceptibility in genes encoding adhesion molecules and DISC1 may result in impairment of brain development. Our data has shown that DISC1 expressed in the developing cerebral cortex, hippocampus and cerebellum of rat brain. N-cadherin and β1-integrin also express in the developing cerebral cortex and hippocampus, which suggesting that DISC1 might be involved in neuronal migration, formation of axon, dendrite and spine and synaptic plasticity by regulating these adhesion molecules in such areas. To clarify this possibility, investigating the alteration of the expression and functions of adhesion molecules in DISC1 transgenic or knockout mice is necessary. In addition, N-cadherin and β1-integrin express not only in neurons but also in glial cells and regulate the differentiation of radial glial cells and oligodendrocytes. In recent report, DISC1 also expresses in these glial cells. Further studies are needed to clarify the role of DISC1 and adhesion molecules in glial cells in brain development.

Recent several studies have reported that MDD impair OLs function, for example, decrease of myelin basic protein (Honer et al., 1999), reduction of corpus callosum of female depression patients (Lacerda et al., 2005), the low density of total glia and OLs in amygdala (Hamidi et al. 2004), and the reduction of the expression of OL-related genes in the temporal cortex (Aston et al., 2005). Furthermore, recent our study indicated that the SGK1–NDRG1–adhesion molecules activation causes excess arborization of OL processes and this abnormality in the OL is related to depression-like symptoms (Fig. 6.). Elucidating the functional roles of the SGK1-NDRG1-adhesion molecules pathway in the OLs is a primary goal of future study for the pathogenesis of MDD.

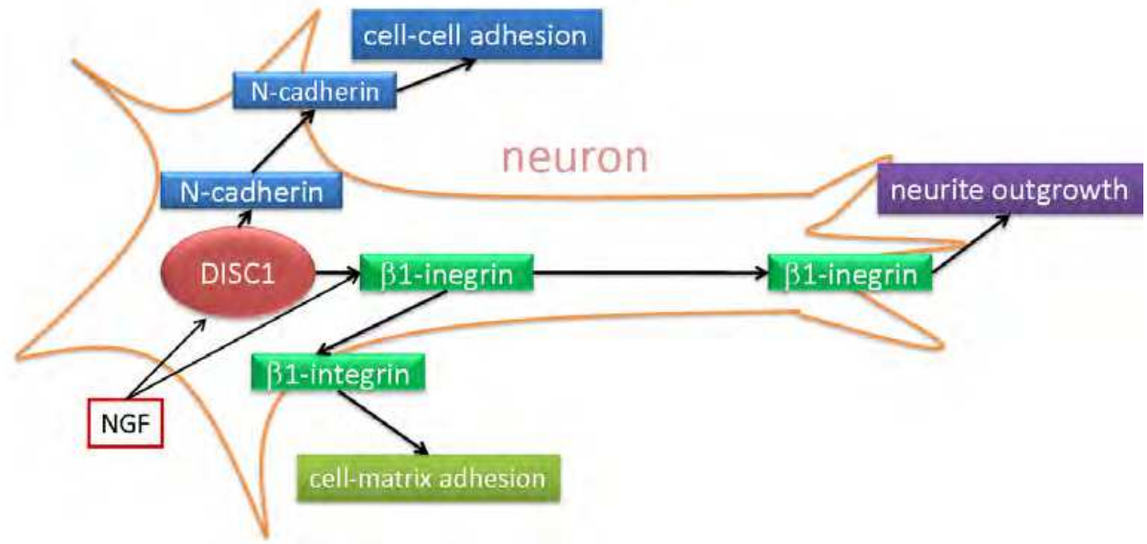


Fig. 6. DISC1 enhances cell-cell adhesion via increasing N-cadherin expression at the cell-cell contact. DISC1 also increases the expression of β1-integrin at the cell surface, which enhances cell-matrix adhesion and neurite outgrowth. Both DISC1 and β1-integrin are positively regulated by Nerve Growth Factor (NGF).

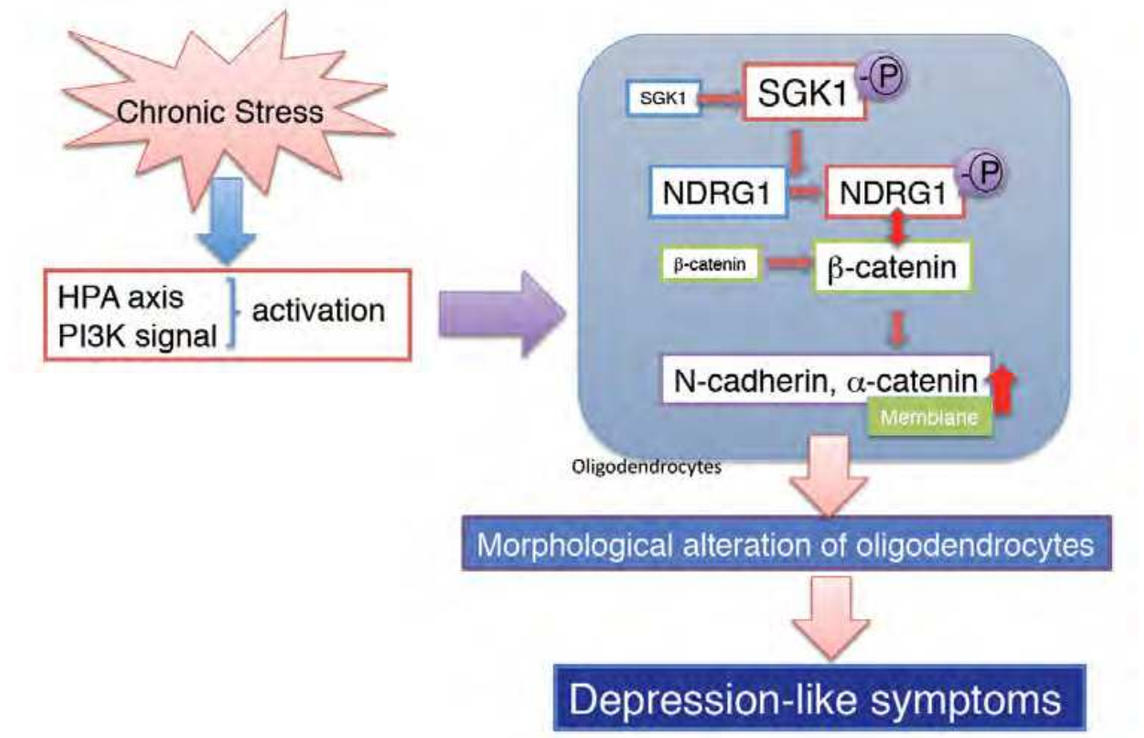


Fig. 7. Elevation of corticosterone induced by chronic stress induce the adherent molecules and morphological change in the oligodendrocytes of corpus callosum via the activation of SGK1-NDRG1 pathway. (Adapted with permission from Miyata et al. 2011.)

5. Acknowledgement

This work has been supported in part by the Osaka Medical Research Foundation for Incurable Diseases, a Grant-in-Aid for Scientific research from Japan Society for the Promotion of Science, a Grant-in-Aid for Scientific Research on Innovative Areas "Neural Diversity and Neocortical Organization" and the Global COE Program from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of Japan and a grant from Dainippon Sumitomo Pharma Co. Ltd.

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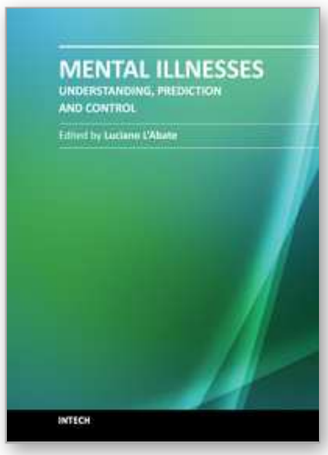
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Mental Illnesses - Understanding, Prediction and Control
Edited by Prof. Luciano LAbate

ISBN 978-953-307-662-1
Hard cover, 458 pages
Publisher InTech
Published online 05, January, 2012
Published in print edition January, 2012

In the book "Mental Illnesses - Understanding, Prediction and Control" attention is devoted to the many background factors that are present in understanding public attitudes, immigration, stigma, and competencies surrounding mental illness. Various etiological and pathogenic factors, starting with adhesion molecules at one level and ending with abuse and maltreatment in childhood and youth at another level that are related to mental illness, include personality disorders that sit between mental health and illness. If we really understand the nature of mental illness then we should be able to not only predict but perhaps even to control it irrespective of the type of mental illness in question but also the degree of severity of the illness in order to allow us to predict their long-term outcome and begin to reduce its influence and costs to society. How can we integrate theory, research evidence, and specific ways to deal with mental illness? An attempt will be made in the last conclusive chapter of this volume.

How to reference
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Tsuyoshi Hattori, Shingo Miyata, Akira Ito, Taiichi Katayama and Masaya Tohyama (2012). Psychosis and Adhesion Molecules, Mental Illnesses - Understanding, Prediction and Control, Prof. Luciano LAbate (Ed.), ISBN: 978-953-307-662-1, InTech, Available from: http://www.intechopen.com/books/mental-illnesses-understanding-prediction-and-control/psychosis-and-adhesion-molecules

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