CIN85 defect in brain and neurobehavioral disorder: involvement in excess dopamine signaling

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Abstract
The Cbl-interacting protein of 85 kDa (CIN85) belongs to a family of ubiquitously expressed adaptor/scaffold proteins. CIN85 interacts with endocytotic proteins involved in various receptor signaling pathways. Despite extensive investigations of CIN85 in receptor trafficking, little is known about its functions in vivo. Mice deficient in brain-specific CIN85 expression show hypereracive phenotypes, which in many ways resemble the behavioral aberrations displayed in human beings affected by attention deficit/hyperactivity disorder (ADHD), a disorder strongly associated with abnormal dopamine signaling. ADHD is a neurobehavioural disorder characterized by either significant difficulties of inattention or hyperactivity and impulsiveness or a combination of the two. While genetic factors are strongly implicated in the etiology of ADHD, the genes responsible for ADHD are unknown. Here, we review the recent progress of CIN85 study and the possibility of ADHD onset owing to CIN85 defect in the brain.

Keywords: CIN85, dopamine signaling, CIN85 deficient mouse, attention deficit/hyperactivity disorder

Introduction
Adaptor proteins are noncatalytic polypeptides that contain one or more domains that are capable of binding to other proteins or nonprotein ligands [1]. These molecules are essential for intracellular signal transduction involved in the regulation of endocrine action, metabolic activity, neuronal function, and cell growth. Recently, there has been growing evidence that adaptor proteins play critical roles in neurobehavioral control. Glutamate receptor interacting protein 1 (GRIP1) regulates social behavior and modulates the autistic phenotype [2]. Maiya et al., reported [3] that a Lin11, Isl-1, and Mec-3(LIM) adaptor protein, LIM domain only protein 4 (LMO4), regulates fear learning. The G protein-coupled receptor kinase-interacting protein-1(GIT1) deficiency in mice causes psychostimulant-responsive attention deficit/hyperactivity disorder (ADHD)-like phenotypes [4].

The Cbl-interacting protein of 85 kDa (CIN85) is a multidisector protein containing three Src homology (SH)3 domains, a proline-rich region and a coiled-coil domain [5]. CIN85 was shown to link Cbl-epidermal growth factor receptor (EGFR) complexes with endophilin-dependent receptor endocytosis in striatal neurons [6]. Recently, we have reported a novel in vivo function of CIN85 in the regulation of postsynaptic dopamine receptor endocytosis in striatal neurons [7]. Mice deficient in CIN85 (CIN85<sup>Δex2</sup>, lacking CIN85 exon 2) expression show ADHD phenotypes. As a molecular explanation of this phenotype, we concluded that the absence of striatal CIN85 causes insufficient complex formation of endophilins with dopamine receptors in the striatum and ultimately decreases dopamine receptor endocytosis in striatal neurons in response to dopamine stimulation.

ADHD is one of the most common childhood disorders and can continue through adolescence and adulthood. Symptoms include difficulty staying focused and paying attention, difficulty controlling behavior, and hyperactivity [8]. It has not been clear until now what causes ADHD. Various factors have been suggested, and genes are believed to play a critical role in ADHD onset [9].

In the present review, we briefly describe a novel function of the adaptor/scaffold protein CIN85 in the regulation of neurobehavior and the possibility of ADHD onset owing to CIN85 defect in the brain.

Structure and function of CIN85
CIN85 was independently identified as CIN85 [5], regulator of ubiquitous kinase (Ruk) [10], SH3-domain-containing gene expressed in tumorigenic astrocytes (SETA) [11] and SH3 domain kinase binding protein 1 (SH3KBP1) [12]. These genes were isolated from either human (CIN85), rat (Ruk and SETA) or mouse (SH3KBP1) sources and show between 92% and 97% sequence identities, suggesting that they represent homologues of one gene. The CIN85 gene is localized on the short arm of the X chromosome (Xp22.1-p21.3) and its length is approximately 353.7 kb in humans (http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene&cmd=retrieve&dopt=full_report&list_uids=30011). The main 3.2 kb CIN85 mRNA is expressed in all adult and newborn tissues [5,10]. Owing to alternative splicing and the use of different promoters, multiple CIN85 mRNA signals have been detected, which showed a more restricted pattern of expression [10]. CIN85 is composed of three N-terminal SH3 domains, followed by a centrally located proline-rich region and a C-terminal coiled coil domain [13]. Initially, CIN85 was identified as a negative regulator of EGFR signaling and phosphoinositide 3-kinase (PI 3-kinase) signaling pathways via its interaction...
with c-Cbl [5,10]. Then, CIN85 was identified as a central adaptor molecule involved in the recruitment of the endocytic machinery required for the internalization of various cell surface receptors, including receptor tyrosine kinases such as EGFR [6,14], hepatocyte growth factor receptor (HGFR, Met) [15], and vascular endothelial growth factor receptor (VEGFR) [16], and also immunoglobulin IgE receptors in mast cells [17]. Recently, it has been reported that CIN85 is involved in the regulation of the immune system and cytokinesis. Using B cell-specific CIN85 knockout mice, Kometani et al., [18] found that CIN85 links the B cell receptor to IkB kinase-β/nuclear factor-kappa B(IKK-β/NFκB) activation, thereby contributing to T cell-independent immune responses. Haglund et al., [19] reported that Cindr, a Drosophila CD2AP/CIN85 ortholog, interacts with Anillin and that depletion of either Cindr or Anillin gives rise to binucleate cells and fewer intercellular bridges in vivo; therefore, Cindr is involved in complete and incomplete cytokinases in Drosophila. In the future, on the basis of these reports, a novel function of CIN85 may be identified since CIN85 is expressed ubiquitously.

Hyperactivity phenotypes of CIN85-deficient mice
Recently, we have found a novel function of CIN85 in the regulation of the signaling associated with behavior [7]. In the mouse brain, the two major isofoms expressed, CIN85-xl and CIN85-l, were found to be abundant in most brain regions examined [7,20]. Interestingly, CIN85-xl is expressed only in the central nervous system (CNS). Furthermore, CIN85 colocalizes with postsynaptic density protein 95 (PSD-95) at postsynaptic sites in the somatodendritic compartment, in which it frequently clustered in dendritic shafts, as well as within dendritic spines [7]. Dendritic spines are small protrusions extending from the surface of dendrites, which are believed to be the main sites of excitatory synapses and are thus vital centers for synaptic transmission in the brain [21]. To investigate the function of CIN85 in the CNS, we generated

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**Figure 1.** A schematic model for the involvement of CIN85 in the internalization of dopamine receptors. CIN85 localizes to the postsynaptic compartment of striatal neurons where it co-clusters with dopamine receptors. CIN85 interacts with endocytic regulators such as dynamin, β-arrestin, and endophilins in the striatum (left panel). The absence of striatal CIN85 causes insufficient complex formation of endophilins with dopamine receptors in the striatum and ultimately attenuates dopamine receptor endocytosis in striatal neurons in response to dopamine stimulation. The defect of dopamine receptor endocytosis induces hyperactivity (right panel) [7].
mice deficient in the two major CIN85 isoforms expressed in the brain (CIN85-xl and CIN85-l) [7]. By homologous recombination, we deleted exon 2 of the CIN85 genomic locus (CIN85\textsuperscript{△ex2}). As expected, all CIN85 protein variants encoded by transcripts initiated from promoter #1 (CIN85-xl, CIN85-l, and the shorter CIN85-D\textsuperscript{ACP}) were abolished in CIN85\textsuperscript{△ex2} mice.

CIN85\textsuperscript{△ex2} mice are viable and fertile, and display no obvious abnormalities in appearance. We subjected the CIN85\textsuperscript{△ex2} mice to extensive analyses of a broad range of parameters in accordance with the physiological screens defined by the German Mouse Clinic (http://www.mouseclinic.de/). Among the parameters tested, the mice showed a clear knockout-specific phenotype in behavior. When subjected to the modified hole-board test [22], which assesses spontaneous behavior such as forward and vertical locomotor activity, speed of movement, and exploratory behavior in a novel environment, the CIN85\textsuperscript{△ex2} mice showed significantly increased activities, as compared with the wildtype. Specifically, the CIN85\textsuperscript{△ex2} mice exhibited increased forward locomotor activity, as manifested by increases in total distance travelled, number of line crossings, mean and maximum velocities, as well as turning frequency. In addition, CIN85\textsuperscript{△ex2} mice showed enhanced exploratory behavior, namely, entering the board more frequently and exploring a larger number of holes on the board than the wild-type mice.

Involvement of CIN85 in dopamine receptor endocytosis
The genetics behind behavioral traits such as locomotor activity and exploratory ambition is undoubtedly highly complex and involves a multitude of pathways, among which dopaminergic, serotonergic and noradrenergic signaling pathways are frequently quoted [23]. On the basis of many studies on the involvement of dopaminergic signaling in the regulation of movement, learning, reward-seeking behavior and motivation [24], together with the rich clustering of dopamine receptors in dendritic spines [25-27], we investigated whether CIN85 could be involved in the regulation of such pathways.

Interestingly, the CIN85\textsuperscript{△ex2} mice display abnormally high levels of dopamine and D2 dopamine receptors (D2DRs) in the striatum [7], an important center for the coordination of animal behavior. Importantly, CIN85 localizes to the postsynaptic compartment of striatal neurons, in which it co-clusters with D2DRs. Moreover, it interacts with endocytic regulators such as dynamin and endophilins in the striatum. In neurons of the wild-type mice, CIN85 resides postsynaptically and associates with endocytic regulators, such as dynamin and endophilins, and it clearly has a crucial function in stabilizing endophilin binding to D2DRs in the striatum. The internalization of D2DRs is caused by the coordination of these endocytic proteins. As a result, dopamine signals are attenuated, and then the appropriate locomotor activity is maintained (Figure 1, left panel). As a consequence, the absence of CIN85 gives rise to insufficient endocytic internalization of D2DRs owing to the lack of endophilin recruitment to the endocytic complex after dopamine stimulation, increasing striatal dopamine receptor levels, which can, at least in part, explain the enhanced locomotor and exploratory behavior we observe in the CIN85\textsuperscript{△ex2} mice (Figure 1, right panel). The resulting increase in the expression levels of surface-associated D2DRs in CIN85\textsuperscript{△ex2} mouse striatal neurons and the ensuing hyperactivity phenotype are in line with earlier findings, showing that activation of postsynaptic D2DRs results in increased locomotor activity and that D2DR knockout mice display reduced spontaneous movements [28,29].

ADHD and genetic aspects
ADHD is the most common behavioral disorder of childhood, affecting 8-12% of children around the world [30,31]. The disorder is defined as a persistent syndrome characterized by inattention, excessive motor activity, and impulsivity [32]. The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) published by the American Psychiatric Association. While the etiology of ADHD seems to be primarily a genetic factor, the disorder does not seem to be caused by a single-gene defect. Currently, as argued by many researchers, ADHD cases may arise from a combination of various genes, many of which affect neurotransmitter signaling, synthesis and modification. Candidate genes include D4 dopamine receptor (D4DR) [32-34], D5 dopamine receptor (D5DR) [35-37], dopamine transporter 1 (DAT1) [38,39], 5-hydroxy-tryptamine transporter (5-HTT, serotonin transporter) [34,40,41], arrestin β-2 [39], phenylethanolamine N-methyltransferase (PNMT) [39] and monoamine-oxidase A (MAOA) [42]. More recently, Arcos-Burgos et al., [43] have reported that a linkage study using worldwide samples (total n=6360, with 2627 ADHD cases and 2531 controls) discovered a genome region in the latrophilin 3 gene (LPHN3), and the statistical association of LPHN3 and ADHD was confirmed.

Currently, there is no information on whether ADHD patients have the mutation/deletion of the CIN85 gene. However, as mentioned earlier, the loss-of-function of CIN85 in the brain causes hyperactivity in mice through the defect of dopamine receptor endocytosis. The molecular defects underlying the onset of ADHD have not been fully characterized, but may include alterations in the expression levels of dopamine ligands and receptors, as well as defects in downstream signaling events [44,45].

CIN85 is a novel regulator of dopamine receptor endocytosis, involved in controlling behavior, and the use of CIN85\textsuperscript{△ex2} mice can lead to new developments in ADHD research.

Abbreviations
ADHD: attention deficit/hyperactivity disorder
CD2AP: CD2-associated protein
CIN85: Cbl-interacting protein of 85 kDa
CNS: central nervous system
DAT1: dopamine transporter 1
DR: dopamine receptor
EGFR: epidermal growth factor receptor
GIIT1: G protein–coupled receptor kinase–interacting protein 1
GRIP1: glutamate receptor interacting protein 1
HGF: hepatocyte growth factor receptor
5-HTT: 5-hydroxytryptamine transporter
IKK-β/NFκB: IκB kinase-β/nuclear factor-kappa B
LIM: Lin11, Isl-1 and Mec-3
LMO4: LIM domain only protein 4
LPIN3: Linternin 3
MAOA: monoamine oxidase A
PI 3-kinase: phosphatidylinositol 3-kinase
PNMT: phenylethanolamine N-methyltransferase
PSD-95: postsynaptic density protein 95
Ruk: regulator of ubiquitous kinase
IKK-β /NFkB: IkB kinase-β/nuclear factor-kappa B
VEGFR: vascular endothelial growth factor receptor
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