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Critical Review

The Roles of Diacylglycerol Kinases in the Central Nervous System: Review of Genetic Studies in Mice

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Abstract. Diacylglycerol kinase (DGK) is an enzyme that converts diacylglycerol to phosphatidic acid. To date, 10 isoforms of DGKs (α, β, γ, δ, ε, ζ, η, θ, ι, and κ) have been identified in mammals, and these DGKs show characteristic expression patterns and roles. The expression levels of DGKs are comparatively higher in the central nervous system than in other organs and may play several important roles in regulating higher brain functions. Currently, many studies have been performed to reveal the roles of DGKs by knocking down or overexpression of DGKs in vitro. Additionally, knockout or overexpression mice of several DGKs have been generated, and phenotypes of these mice have been studied. In this review, we discuss the roles of DGKs in the central nervous system based on recent findings in genetic models.

Keywords: central nervous system, diacylglycerol kinase, genetic mouse, mood disorder

1. Introduction

After Gq protein–coupled receptors are stimulated, phospholipase C is activated and produces diacylglycerol (DG) from inositol phospholipids (1). DG is an essential second messenger in mammalian cells and plays important roles in gene transcription, lipid signaling, cytoskeletal dynamics, intracellular membrane trafficking, and neurotransmitter release (2, 3).

Diacylglycerol kinase (DGK) is an enzyme that phosphorylates DG to phosphatidic acid (PA), which means that DGK terminates DG signaling and initiates PA signaling. Similarly to DG, PA also regulates various types of intracellular signaling such as mammalian target of rapamycin and Raf-1 kinase (4 – 6). From these reports, DGK is one of the main molecules regulating intracellular signaling. To date, 10 mammalian DGKs have been identified (7 – 16). DGKs are known to be strongly expressed in the central nervous system, but the expression patterns are different for each isoform (17 – 20). Additionally, each DGKs isoform has a distinguishing localization in cells (21, 22), suggesting that DGKs play unique roles in each isoform.

To demonstrate the functions of DGKs, many studies have been performed using a genetic approach in vitro and in vivo. To date, several overexpression- or knockout (KO)-mice have been generated by many research groups: DGKα-KO (23), cardiac-specific overexpression of DGKα (24), DGKβ-KO (25), DGKδ-KO (26), DGKε-KO (27), DGKζ-KO (28), and DGKι-KO mice (29). From the phenotypes of these DGK-KO mice, each DGK has been shown to play an important roles in regulating various neuronal functions such as cognitive functions (25, 30, 31) , mood (32), and resistance to excitatory stimuli (33 – 35).

In this review, we discuss the roles of DGKs in the central nervous system from recent findings employing genetic models and mention the possibility of involvement in several diseases.

2. Isoforms of DGKs and their classification

To date, 10 mammalian DGKs have been identified (7 – 16, 36), and they are classified into five types (Fig. 1). All DGKs have cysteine-rich domains and catalytic domains.

DGKα, β, and γ possess EF-hand structures and recoverin homology domains, and they are classified as type I DGKs (37). EF-hand structures have a Ca^{2+}-

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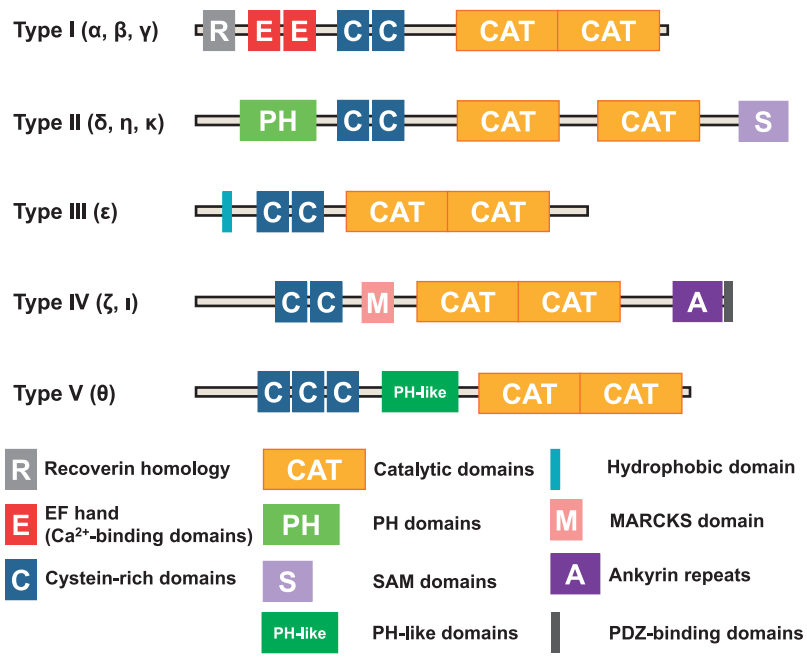

Fig. 1. The structures of DGKs. DGK isoforms are classified into five types.

binding activities; therefore, Ca^{2+} induces conformational changes and regulates the kinase activities of type I DGKs.

DGKδ, η, and κ possess pleckstrin homology (PH) domains and sterile α motifs (SAM) domains and are classified as type II DGKs (10 – 12). The PH domain of DGKδ have affinities for inositol 1,4,5-trisphosphate and 1,4,5,6-tetrakisphosphate (38). The SAM domain binds zinc at multiple sites and cause the oligomarization of type II DGKs (39 – 41). Furthermore, both the SAM and N-terminal PH domains of DGKδ are needed to exert their own effects on endoplasmic reticulum-to-Golgi traffic (42).

DGKε is the only type III isoform; it possesses a hydrophobic domain (43) and differs in showing the selectivity for acyl chains (44, 45).

DGKζ and ι are classified as type IV DGKs. They contain myristoylated alanine-rich protein kinase C substrate (MARCKS), PDZ-binding, and ankyrin domains. The MARCKS domain is homologous to the phosphorylation-site domain (PSD) of the MARCKS protein and regulates the nuclear localizations of DGKζ (46, 47). The PDZ-binding and ankyrin domains of DGKζ regulate interactions with several proteins (48 – 51).

DGKθ is classified as type V DGK and possesses three cysteine-rich domains and a PH-like domain (16).

3. Type I DGKs in the central nervous system

3.1. DGKα

In the central nervous system, type I DGK is expressed in various regions (Table 1). DGKα was isolated from a rat brain cDNA library by Goto et al. (7) and was found to be expressed specifically in the oligodendrocytes, but not neurons. Gene expression profiling of a mouse brain has shown that DGKα is expressed throughout the entire brain (17). In the retinas, DGKα is also expressed in ganglion cells in the ganglion cell layer (GCL) and inner plexiform layer (IPL) (18).

DGKα KO mice were generated by Olenchock et al. (23) and actively used to investigate the involvement of DGKα in the immune system (23, 52, 53). There are no differences in the birth rate, body weight, and normal behavior (such as locomotor activity, anxiety levels, and cognitive functions) between DGKα KO and wild-type mice (unpublished data, M. Ishisaka, Y. Shirai, and H. Hara). However, the inflammatory response is also involved in various diseases of the central nervous systems (54); therefore DGKα KO mice might show unique phenotypes under conditions of stress.

3.2. DGKβ

DGKβ is strongly expressed in the olfactory bulb, cortex, striatum, and hippocampus, but not in the thalamus, hypothalamus, or most brainstem nuclei (Table 1); its expression is detected mainly in neurons

Table 1. Expression patterns of DGKs in a rat or mouse brain

Isoforms	Olfactory bulb	Cortex	Striatum	Hippocampus	Cerebellum	Representative references
α	○	○	○	○	○	(61)
β	◎	◎	◎	◎	N.D.	(8)
γ	○	○	N.D.	◎	◎	(61), (62)
δ	N.D.	○	N.D.	○	○	(33)
η	◎	◎	◎	◎	◎	(17)
κ	N.D.	N.D.	N.D.	N.D.	N.D.	(17)
ε	○	—	—	◎	◎	(61), (64)
ζ	○	○	—	◎	◎	(14), (61)
ι	○	○	○	◎	○	(15), (76)
θ	○	○	N.D.	◎	◎	(16)

Double circle, strongly expressed; Circle, moderately or weakly expressed; N.D., not detected.

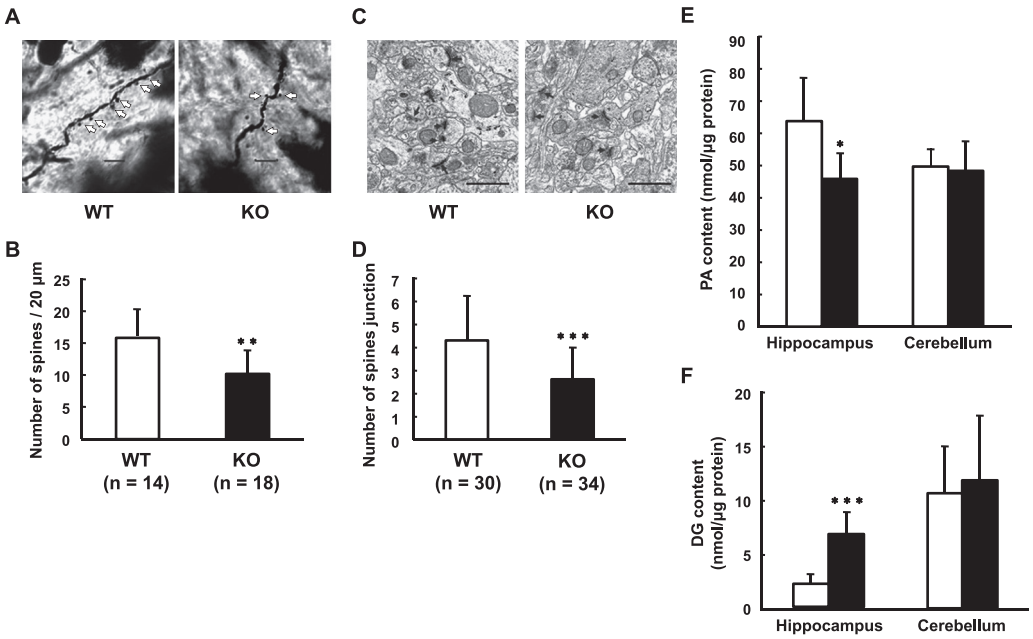

Fig. 2. Abnormalities in the hippocampus of DGKβ KO mice. A) Typical images of Golgi staining of hippocampal neurons at CA1 regions of WT and DGKβ KO mice. Yellow arrows show spines. Scale bar = 5 μm. B) The number of synapses in the CA1 hippocampal region was counted (WT, n = 14; KO, n = 18). C) Typical images of electron microscopy (× 243,000). Scale bar = 5 μm. D) The number of synaptic junctions with PSD in the micrographs was counted (WT, n = 40; KO, n = 40). Red arrows indicate synaptic junctions. E, F) PA or DG level in the hippocampus and cerebellum from WT or DGKβ KO mice. The results were cited from ref. 25.

(8). In the retinas, DGKβ is strongly expressed in the rod and cone bipolar cells and horizontal cells of the outer plexiform layer (OPL) and moderately expressed in the inner nuclear layer (INL) and IPL (18).

DGKβ KO mice were generated by Shirai et al. in 2010 (25). Based on their behavioral analysis, DGKβ KO mice exhibit cognitive impairment, mania-like behavior, and increased seizure susceptibility (25, 32, 55). DGKβ has been reported to show unique membrane localization and its expression levels in rat brains rapidly increases after postnatal day 14 (56, 57), when synaptic formation is progressing. In the hippocampus and striatum, DGKβ is accumulated at the perisynapse of dendritic spines (58, 59). In the hippocampus of DGKβ KO mice, the numbers of spines and spine junction are lower than those of wild-type mice, with decreasing PA content and increasing DG content (Fig. 2). Additionally, in the primary cultured hippocampal neurons from DGKβ KO mice, branching and spine formation have been found to be decreased and ameliorated by DGKβ over-

expression (25). These results suggest that DGKβ plays an important role in synaptic formations, which is consistent with another study (59).

In the hippocampal CA3 area of DGKβ KO mice, the numbers of parvalbumin-positive interneurons decreased, which may contribute to the increment of seizure susceptibility toward kainic acid and pentylenetetrazol (55). In the cortex of DGKβ KO mice, cortical spine density has been found to be significantly decreased and Akt-GSK3β signaling was impaired, which may be a strong contributor to mania-like behavior such as hyperlocomotion, reduced anxiety, and reduced depression (32). It was reported that the splice variant at the COOH-terminal of DGKβ was related to bipolar disorder (57). Furthermore, the abnormal behaviors of DGKβ KO mice were partly reversed using lithium or methylphenidate treatment (32, 60); therefore, DGKβ KO mice may be a useful animal model for bipolar disease and attention deficit/hyperactivity disorder.

From these findings, DGKβ deficiency may affect brain development and lead to abnormal neuropsychiatric behaviors in adult mice. Furthermore, DGKβ is also involved in the molecular machineries of dendrite outgrowth and spinogenesis of neurons.

3.3. DGKγ

DGKγ is expressed strongly in the cerebellum and moderately in the hippocampal pyramidal cells and dentate granule cell layer. The expression is also detected in the cortex and olfactory bulb (61, 62). The expression of DGKγ in the brain is gradually increased after birth, like it is for DGKβ (56). DGKγ does not seem to be expressed in the retina (19). To date, there are no reports of deficient mice.

4. Type II DGKs

4.1. DGKδ

Sakane et al. reported that DGKδ is not expressed in the central nervous system in humans, including the brain and retina (10). However, Leach et al. reported that DGKδ is expressed prominently in pyramidal neurons of the neocortex and hippocampus, as well as within internal granule cell neurons of the cerebellum (33).

DGKδ KO mice were generated by Crotty et al. in 2006 (26). The mouse pups were born with open eyelids and died shortly after birth (within 24 h), which is similar to epidermal growth factor receptor (EGFR) KO mice (26). It has been reported that DGKδ heterozygous mice develop insulin resistance (63) and that DGKδ also affects the EGFR by modulating PKC signaling (26). Taken together, these findings indicate that DGKδ has the potential of regulating the downstream signaling of numerous other tyrosine kinase–type receptors.

Kohyama-Koganeya et al. reported that a female patient with a de novo balanced translocation, 46,X,t(X;2)(p11.2;q37)dn, exhibited seizures, capillary abnormalities, developmental delays, infantile hypotonia, and obesity (64). DGKδ is disrupted at 2q37 and involved in central nervous system development and function (33). Mice with DGKδ disruption in the DGAP095 showed abnormal epileptic discharges, and DGKδ is also involved in the etiology of seizures. However, the roles of DGKδ in these conditions remain relatively unknown.

4.2. DGKη

There exist two isoforms (η1 and η2) and DGKη1 mRNA has been reported to be ubiquitously distributed in various tissues including the brain (40). A previous report suggested the correlation between bipolar disorder and DGKη (65 – 67). In the patient with bipolar disorder, increased DGKη mRNA levels (66) and four SNPs in the DGKη (67) were reported. Overexpression or mutation of DGKη may allow researchers to reveal the involvement of DGKη in the pathogenesis of bipolar disorder.

The expression patterns of DGKκ were revealed, but its function has not been elucidated (11, 17).

5. Type III DGKs

5.1. DGKε

DGKε is abundantly expressed in the retina, especially in the INL, outer nuclear layer (ONL), and inner segment layer (ISL), and it is the only isoform expressed in photoreceptors (18, 19, 64). In the brain, DGKε is also expressed and distributed in the Purkinje cells of the cerebellum, the pyramidal cells of the hippocampus, the mitral cells of the olfactory bulb, and the neurons of the substantia nigra (27, 64).

DGKε KO mice were generated by Rodriguez et al. in 2001 (27). As discussed, DGKβ, DGKδ, or DGKζ deficiency (which is noted in a later chapter) exacerbated seizure phenotypes, but DGKε KO mice showed a higher resistance to seizures induced by electroconvulsive shock (27, 34). DGKε is the only DGK to exhibit high selectivity for arachidonate-containing substrates (13). Further, in DGKε KO mice, the phosphatidylinositol 4,5-bisphosphate-signaling pathway in the cerebral cortex was greatly affected, leading to lower accumulation of 20:4-DAG and free 20:4, and seizures were decreased compared with wild-type mice (27). In normal conditions, DGKε-KO mice had lower PI content with 1-stearoyl-2-arachidonoyl acyl chains (68).

In the striatum of R6/2 Huntington disease transgenic mice and Hdh 111Q/111Q cells (a mouse Huntington disease striatal cell model), the expression levels of

DGKε have been found to increase. Furthermore, the knockdown of DGKε or pharmacological inhibition using DGK inhibitor I (also known as R59022) significantly ameliorates the toxic effects of expanded Huntingtin in *Drosophila* and Hdh 111Q/111Q cells (69). Further research is needed to reveal the roles of DGKε using DGKε KO mice.

6. Type IV DGKs

6.1. DGKζ

DGKζ is expressed strongly in the cerebellum, hippocampal pyramidal and dentate granular cells, olfactory bulb, and dense cerebral cortex (14). Furthermore, in the retinas, DGKζ is expressed in the GCL, OPL, INL, and IPL and localized in rod and cone bipolar cells, horizontal cells, amacrine cells, and ganglion cells (18, 19).

DGKζ KO mice were generated by Zhong et al. in 2003 (28). In hippocampal slices of DGKζ-KO mice, PA production has also been found to decrease after stimulation, and the spine density of hippocampal CA1 pyramidal neurons are significantly reduced, suggesting that DGKζ is required to maintain dendritic spines (30). Furthermore, Schaffer collateral-CA1 pyramidal synapses in the hippocampus of DGKζ-KO mice showed enhanced long-term potentiation (LTP) and attenuated long-term depression (LTD) (70). In dendric spine maintenance, DGKζ also plays an important role by not only affecting the PA production, but also interacting or forming a multi-protein complex with PSD-95, p21-activated kinase 1 (PAK1), RAS-related C3 botulinus toxin substrate 1 (Rac1), and others (30, 71). However, the behavioral analysis of cognitive function or other higher brain functions has not yet been reported and therefore, further research is needed to confirm DGKζ's involvement in brain function.

After several excitatory stimuli, the localization of DGKζ has been found to change dramatically from the nucleus to the cytoplasm and degraded (72 – 74). DGKζ is involved in early events of the apoptotic cell death pathway. Indeed, in DGKζ KO mice, kainic acid has caused serious convulsive seizures and neuronal cell death in the hippocampus compared with wild-type mice (35). On the other hand, DGKζ-immunoreactivity is also detected in non-neuronal cells such as microglia in pathological conditions (75). These findings indicate that DGKζ plays several important roles in non-neuronal cells.

6.2. DGKι

DGKι is expressed in the brain and retinas (15). In the brain, DGKι is strongly expressed in the hippocampal calcium region and dentate gyrus, and it is moderately expressed in the cortex and striatum (76). In the retinas, its expression is detected mainly in the postsybaptic region of rod bipolar dendrites in the OPL (18).

DGKι KO mice were generated by Regier et al. in 2005 (29). In the hippocampus of these mice, there is a small increase in the presynaptic release probability and a reduction in metabotropic glutamate receptor–dependent LTD, although their dendritic spines are not affected. The behavioral analyses indicate that DGKι-KO mice seemed to take more time to habituate to a novel environment, but there are no changes in their locomotor activity, anxiety-like behavior, or spatial learning and memory (31). In another study, it has been reported that the expression levels of DGKι are up-regulated in the cortex of alcohol- accepting rats compared with alcohol non-accepting rats (76). These findings indicate that DGKι-KO mice exhibit different phenotypes in various behavioral tests such as alcohol-accepting tests.

7. Type V DGKs

DGKθ is expressed strongly in the cerebellar cortex and hippocampus, and it is moderately in the olfactory bulb and brain stem nuclei (16). The expression of DGKθ during the orgnanogenesis of mouse embryos has been studied in detail (77). DGKθ is expressed prominently in the brain during the early stage of development and these results may demonstrated the potential of the involvement in the development of the brain. However, at present, there are no reports that have discussed its expression in the retina or its function.

8. Discussion

In this review, we discussed the roles of DGKs in the central nervous system, which have been revealed mainly from genetic models.

DGKβ and DGKζ are comparatively well studied, but other isoforms have not been investigated extensively. Overall, DGK deficiencies cause an imbalance between DG and PA and affect other types of cellular signalings. However, the role of specific DGKs differ from one another based on their localization or structures.

DGKs are reported to be expressed mainly in the brain, but their expression is also detected in other regions such the retina. However in the central nervous system, most studies were performed to reveal the roles of DGKs in the brain. In *Drosophia*, the rdgA mutatation, which leads to a lack of eye-specific and membrane-associated DGK activity, caused photoreceptor cell degeneration (78). In the other reports, it has been suggested that rdgA is essential for photoreceptor maintenance (79, 80).

Taken together, these findings suggest that DGKs are also important in the retina, but additional research is needed to clarify their roles.

To date, there is no compound that activates or inhibits the limited isoforms of DGKs. Hence, it is essential to understand the roles of DGKs and to generate an activator or inhibitor that exhibits selectivity to each isoform.

9. Conclusion

In the central nervous system, various isoforms of DGKs are expressed and play their own roles, which differ from one to another. It may be useful to understand the roles of each DGK to clarify the pathogenesis of various disorders related to DGKs in the central nervous system.

Conflicts of Interest

The authors declare no conflict of interest.

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