J Pharmacol Sci **114**, 25 – 31 (2010)

Journal of Pharmacological Sciences

Forum Minireview

Advanced Research on Dopamine Signaling to Develop Drugs for the Treatment of Mental Disorders: Proteins Interacting With the Third Cytoplasmic Loop of Dopamine D_2 and D_3 Receptors

Norifumi Shioda[1], Yusuke Takeuchi[2], and Kohji Fukunaga[1,*]

[1]*Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Tohoku University, Sendai 980-8578, Japan*
[2]*Aoba Hospital, Uki, Kumamoto 869-0513, Japan*

Received February 18, 2010; Accepted June 14, 2010

Abstract. Among the various dopamine receptors, D_2-like receptors (D2R, D3R, and D4R) are characterized by a large third cytoplasmic loop, a short carboxyl-terminal tail, and the ability to activate inhibitory G proteins. The diverse activities of D_2-like receptors are partly mediated by proteins that interact with the third cytoplasmic loop, which regulate receptor signaling, receptor trafficking, and stability. Furthermore, in the case of D2R and D3R genes, mRNA splicing generates isoforms in the region of the third cytoplasmic loop. The gene encoding D2R gives rise to two isoforms, termed the dopamine D_2 receptor long isoform (D2LR) and the dopamine D_2 receptor short isoform (D2SR), which lacks 29 amino acids of the D2LR within the third cytoplasmic loop. The D3R gene also produces at least seven distinct alternative splicing variants including D3nf, in which 98 base pairs in the carboxyl-terminal region of the third intracellular loop are deleted. In this review, we focus on proteins interacting with the dopamine D_2/D_3 receptors in the third cytoplasmic loop. We also define a novel binding protein, heart-type fatty acid–binding protein (H-FABP), which specifically interacts with the 29 D2LR amino acids deleted in D2SR and document its function in D2LR signaling.

Keywords: dopamine D_2 receptor, dopamine D_3 receptor, alternative splicing variant, heart-type fatty acid–binding protein, catalepsy

1. Introduction

Dopamine receptors are important molecules underlying neuropsychotic disorders such as Parkinson's disease and schizophrenia. Dopamine receptors are members of the seven transmembrane and trimeric GTP-binding protein (G protein)-coupled receptor family and are classified into distinct subfamilies of D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) receptors based on pharmacological properties, sequence homology, and structure (1). D_1-like receptors exhibit short third cytoplasmic loops and very long carboxyl-terminal intracellular tails. By contrast, D_2-like receptors have long third intracellular loops and short carboxyl-terminal intracellular tails. D_1-like receptors activate adenylyl cyclase by coupling to Gs protein. By contrast, D_2-like receptors are coupled to pertussis toxin (PTX)-sensitive Gi/Go proteins and can mediate several signaling pathways, such as inhibition of adenylyl cyclase, activation of K^+ channels, inhibition of Ca^{2+} channels, and stimulation of Na^+/H^+ anti-porters (2).

Among the dopamine-receptor subtypes, the D_2 receptor (D2R) is most extensively studied since all clinical antipsychotic drugs act as D2R antagonists in the mesolimbic dopamine system, and the abilities of these drugs to block D2R correlate with antipsychotic efficiency. D2R exists as two alternatively spliced isoforms — the dopamine D_2 receptor long isoform (D2LR) and the dopamine D_2 receptor short isoform (D2SR) — that differ in a 29 amino acid insert in the third cytoplasmic loop (3). Human D2R reportedly has a polymorphism changing serine to cysteine at amino acid 311 in the third

*Corresponding author. fukunaga@mail.pharm.tohoku.ac.jp
Published online in J-STAGE on August 12, 2010 (in advance)
doi: 10.1254/jphs.10R02FM

cytoplasmic loop of D2LR (4). That variant is reportedly associated with schizophrenia (5), although studies have failed to confirm these reports (6). Pharmacologically, the human D2R Ser311Cys variant has been shown to be less effective in inhibiting cyclic AMP accumulation than wild-type D2R when expressed in Chinese hamster ovary (CHO) cells (7). A recent study characterized a single nucleotide polymorphism (SNP) within the D2R gene at intron 6, rs1076560 (G > T), in postmortem human striatum and prefrontal cortex (8). The resultant GT genotype is associated with relatively lower expression of D2SR mRNA in prefrontal cortex and striatum, as well as with significantly reduced performance on a cognitive task relative to the GG genotype in humans (8). The gene encoding D3R is also organized to allow for production of different transcripts via alternative splicing, and at least seven distinct D3R splice variants have been identified: full-length D3R; a mouse shorter receptor isoform (D3SR) lacking 21 amino acids within the third cytoplasmic loop, but no correspondence to the human gene, D3 (TM3-del); D3 (TM4-del); D3 (O2-del); rD3in; and D3nf (9). Although both D3R and D3SR exhibit high-affinity dopamine binding, the other five variants do not bind dopamine and are believed to function to regulate receptor dimerization (9). D3nf, which is expressed in human brain, is the most investigated of these with particular attention on the third cytoplasmic loop. D3nf mRNA lacks 98 ribonucleotides that encode the C-terminal region of the third cytoplasmic domain, resulting in a frame shift and giving rise to a novel 55 amino acid sequence in the C-terminus of the protein ends that is not seen in the D3R. This difference includes sequences that comprise transmembrane domains 6 and 7 that are deleted. In humans, dopamine D3R mRNA expression has been shown to be decreased in the cortex of schizophrenia patients, whereas increased D3nf splicing efficiency was observed in the cortex of postmortem tissue from schizophrenia patients (9).

In this review, we summarize what is known about proteins that interact with the third cytoplasmic loop of D2R and D3R in brain (Fig. 1). Alternative splicing of mRNA encoding the loop may also alter interactions of cytosolic and membrane-associated interacting proteins that regulate D_2/D_3-receptor signaling. Understanding both D_2/D_3 receptor–interacting proteins and receptor splice variants may reveal mechanisms underlying disorders related to dopamine system dysfunction.

2. Proteins interacting with the N-terminal region of the third cytoplasmic loop of D2R/D3R: CaM, NR2B, CaMKII, Filamin A, Protein 4.1N, and Par-4

Calmodulin (CaM) acts as a cellular Ca^{2+} sensor to activate ion channels and enzymes that regulate the cell cycle, cytoskeletal organization, and development. Bofill-Cardona et al. reported that there is a CaM-binding motif located in the N-terminus of the third D2R cytoplasmic loop at residues I210 to V223 in vitro (10). This motif exhibits consensus hydrophobic residues (Val, Ile) at I210, I215, and V223 (11). Ca^{2+}/CaM binding to the receptor interferes with D2R signaling by inhibiting receptor-mediated G protein activation. CaM does not perturb G protein recognition but impedes receptor-induced activation (10). By contrast, CaM does not bind to the third cytoplasmic domain fragment of glutathione S-transferase (GST)-D3R (R210 – P239) (12).

N-Methyl-D-aspartate (NMDA) receptors comprise a family of ionotropic glutamate receptors (GluRs) playing a central role in synaptic plasticity and memory formation (13). These receptors form by assembly of the principal NR (NMDA receptor) 1 subunit with different modulatory NR2 subunits (NR2A – D). NR2B selectively binds to D2R, but not to D3R, through an N-terminal 10 amino acid motif, T225 – A234, of the D2R third cytoplasmic domain (14). Although the NR2B binding motif is adjacent to the CaM binding domain at I210 – V223, it does not bind CaM, strongly suggesting that NR2B–D2R interaction does not affect CaM-D2R binding. However, NR2B–D2R interaction disrupts the NR2B – Ca^{2+}/CaM-dependent protein kinase II (CaMKII) interaction, inhibiting NR2B phosphorylation at S1303 by CaMKII (14). Furthermore, the NR2B–D2R interaction inhibits NMDA receptor–mediated currents in medium-sized striatal neurons (14).

CaMKII is highly expressed in the central nervous system, especially in the hippocampal formation (15). CaMKII is a multifunctional protein kinase that regulates biosynthesis and exocytosis of neurotransmitters and synaptic plasticity. CaMKII autophosphorylation converts it from a Ca^{2+}-dependent to a Ca^{2+}-independent species. Elevation of intracellular Ca^{2+} levels in cultured neurons by NMDA-receptor stimulation results in increased CaMKII autophosphorylation at T286 of the α-subunit and T287 of the β-subunit, with concomitant elevation of Ca^{2+}-independent activity. Increased CaMKII autophosphorylation is essential for long-lasting increases in synaptic efficacy seen following long-term potentiation in the hippocampus (16). CaMKIIα directly binds to D3R fragments containing residues R210 to P239, a 30 amino acid region at the N-terminus of the third cytoplasmic loop in vitro (12). The CaMKIIα-

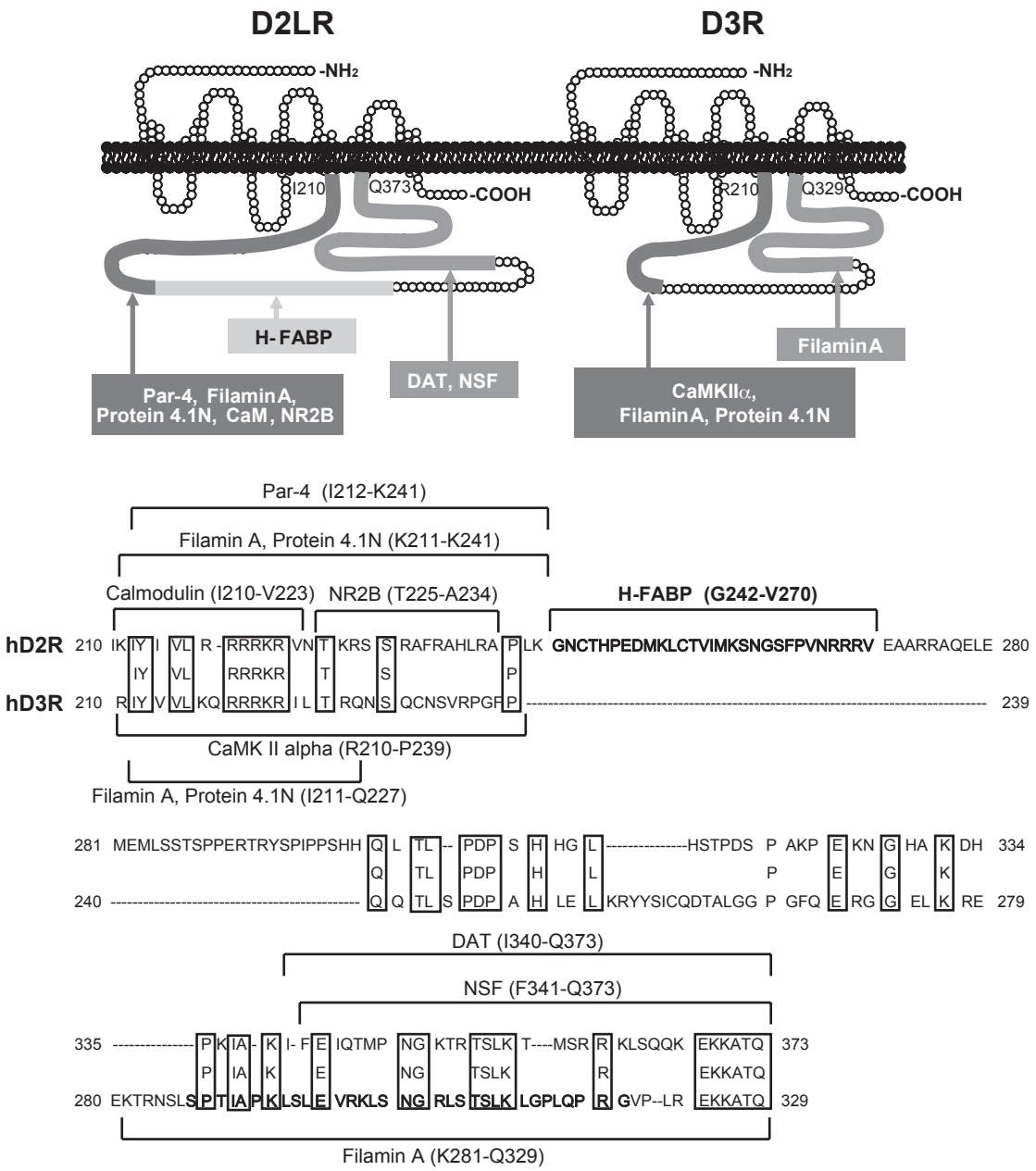

Fig. 1. Primary sequence of proteins interacting with the third cytoplasmic domains of the human D2R (dopamine receptor D_2 isoform long [NP_000786.1]) and human D3R (dopamine receptor D_3 isoform a [NP_000787.2]). Amino acid sequences in bold in hD2R (G242 – V270) and hD3R (S287 – G319) appear in alternatively spliced variants. The dopamine D_2 receptor short isoform (D2SR) [NP_057658.2] lacks a 29 amino acid sequence, which interacts with H-FABP. The dopamine receptor D_3 short isoform (D3SR, D3e) [NP_387512.3] is missing a 33 amino acid segment including the Filamin A–binding domain, which is contained in the dopamine receptor D_3 long isoform (D3a). Amino acid residues conserved in D2R and D3R are boxed. Brackets illustrate binding domains of proteins interacting with both receptors.

interacting region is restricted to the CaMKII*α* catalytic domain. Furthermore, CaMKII*α* phosphorylates D3R at S229 in the R210 – P239 motif. In accumbal neurons in vivo, Ca^{2+} stimulates binding of CaMKII to D3Rs and increases D3R phosphorylation, suppressing D3R function (12).

Filamin A is an actin binding protein that plays an important role in construction of the submembranous cytoskeleton. Filamin A binds to N-terminal regions of the third cytoplasmic loops of D2R and D3R and is thought to be required for proper plasma membrane localization of both receptors (17). Mapping analyses show

that a core sequence of approximately 19 residues within the N-terminal segment of the third cytoplasmic loop of D2R (K211 – K241) and D3R (I211 – Q227) is likely required for Filamin A association, although an additional segment within the C-terminal portion of D3R (K281 – Q329), but not in the D2R third cytoplasmic loop, may also contribute to Filamin A – D3R interaction. Several point mutations in the gene encoding Filamin-A within the region of dopamine-receptor binding have been found to block delivery of expressed dopamine D2R to the plasma membrane, suggesting a key role for this protein in D2R cell surface trafficking (18).

Protein 4.1N is a member of the 4.1 family enriched in neurons and associated with submembrane cytoskeletal elements. The 4.1 family also includes protein 4.1R in erythrocytes and the 4.1G and 4.1B isoforms (19). The 4.1 proteins are critical components of the spectrin–actin cytoskeleton and provide attachment between the cytoskeleton and the cell membrane. Among dopamine receptors, protein 4.1N interacts with the N-terminal portion of the third cytoplasmic loop of D2R (K211 – K241) and D3R (I211 – Q227) (20). The dopamine receptor–binding site on protein 4.1N maps to the C-terminal domain, which is highly conserved among all 4.1 family members, and both D2R and D3R have also been shown to interact with the C-terminal domains of proteins 4.1R, 4.1G, and 4.1B. Co-expression of dopamine D2R or D3R with a mutant form of protein 4.1N that contains the dopamine receptor–binding site but lacks the 4.1N membrane–binding domain decreases cell surface expression of D2R and D3R in mouse neuroblastoma Neuro2A cells, suggesting functional roles for dopamine D2/D3R–4.1N interaction in the localization or stability of dopamine receptors at the neuronal cell surface.

Prostate apoptosis response 4 (Par-4) is a leucine zipper–containing protein initially identified as a proapoptotic factor induced by apoptotic stimuli (21). In the nervous system, Par-4 induction is linked to neuronal cell death in neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. Par-4 was shown to be a D2R-interacting protein in a yeast two-hybrid screen of a human fetal embryonic brain library using the third intracellular loop of human D2LR (I212 – Q373) as bait (22). Furthermore, in vitro binding assays identified the domain of D2R interacting with Par-4 as the first 30 amino acid residues of the third intracellular loop (amino acid residues I212 – K241). Since CaM binds to D2R in the same region (I210 – V223), CaM likely competes with Par-4 to bind D2R in a Ca^{2+}-dependent manner, which would result in reduced D2R efficacy and relieve D2R-mediated inhibition of cAMP signaling (22).

3. Proteins interacting with the C-terminal region of the third cytoplasmic loop of D2R/D3R: NSF and DAT

N-Ethylmaleimide-sensitive factor (NSF) is a homohexameric ATPase (23) that is an essential component of the protein machinery responsible for various membrane fusion events, including intercisternal Golgi protein transport and exocytosis of synaptic vesicles. Direct interaction between the carboxyl tail of the AMPA-receptor GluR2 subunit and NSF has been documented (24). Studies employing co-immunoprecipitation, affinity purification, and in vitro binding assays also show that NSF directly binds to the third cytoplasmic loop of D2R at F341 – Q373 (25). D2R activation increases this interaction, resulting in decreased D2R–GluR2 interaction. This result suggests that NSF regulates interaction between the two receptors, depending on the activation state of the D2R (25).

The dopamine transporter (DAT) is a membrane-bound protein that facilitates reuptake of extracellular DA and is a target for drugs of abuse including cocaine and amphetamine. DAT represents a major presynaptic component involved in regulating dopaminergic tone. Lee et al. provide evidence for direct interaction between the third cytoplasmic loop of D2R (I340 – Q373) and DAT (26). They employed the D2SR isoform in experiments utilizing transfected cells and GST fusion proteins, as DAT interacts with a D2R region common to both D2SR and D2LR. DAT recruitment to the plasma membrane, which is essential for its function, is promoted by the D2R–DAT interaction. Since mice injected with peptides disrupting DAT/D2R association exhibit decreased synaptosomal dopamine uptake and increased locomotor activity (26), interaction between these two proteins may contribute to dopaminergic tone and activity within the brain.

4. H-FABP is a novel protein that interacts with a unique residue of the third cytoplasmic loop of D2LR only

As noted, proteins have been identified as interacting with the D2R third cytoplasmic loop by using yeast two-hybrid systems and in vitro and in vivo binding assays. However, the molecules cited above interact with regions common to the third cytoplasmic loop of D2LR and D2SR. Therefore the 29 amino acid insert (G242 – V270) seen only in D2LR does not participate in these interactions. We have identified for the first time the heart-type fatty acid binding protein (H-FABP, FABP3) as a protein binding to this 29 amino acid domain found only in D2LR using a yeast two-hybrid system (27). When D2LR

or D2SR was co-expressed with H-FABP in neuroblastoma NG108-15 cells, over-expressed and endogenous H-FABP clearly co-localized with only the D2LR protein in the Golgi apparatus but not in the plasma membrane. In immunoprecipitation assay, we confirmed the interaction between H-FABP with D2LR-YFP, but not with D2SR-YFP in transfected NG108-15 cells. Brain-type (B-) FABP did not bind to D2LR-YFP (27). Likewise, the immunocomplex with anti-D2LR antibody using the striatal cell extracts included H-FABP in wild-type mice, but not in H-FABP knockout (KO) mice (28).

The striatal microcircuit is composed of medium-sized spiny neurons that receive excitatory corticostriatal glutamatergic innervation, dopaminergic nigrostriatal fibers, and cholinergic interneuron terminals (Fig. 2). Strong H-FABP immunoreactivity was detected in all cholinergic neurons. H-FABP protein is also expressed in glutamatergic terminals in the dorsal striatum, whereas H-FABP is not present in dopaminergic terminals or in postsynaptic densities in dendritic spines of medium-sized spiny neurons in the dorsal striatum. In H-FABP–expressing regions, D2R was also present in cell bodies of cholinergic neurons and in glutamatergic terminals in the dorsal striatum (28). Interestingly, H-FABP KO mice exhibit D2R dysfunction, based on evaluation of dopamine-related behaviors (28). Specifically, H-FABP KO mice showed reduced responsiveness to methamphetamine (METH)-induced sensitization of locomotor activity compared to wild-type mice. Enhanced haloperidol-induced catalepsy was also observed in H-FABP KO mice compared to wild-type mice. Consistent with the latter findings, aberrant increased acetylcholine (ACh) release and depolarization-induced Glu release were observed in the dorsal striatum of H-FABP KO mice. H-FABP expressed in ACh interneurons and terminals of glutamatergic neurons likely regulates ACh and Glu release in the dorsal striatum of mouse brain through interaction with D2LR. Taken together, H-FABP is highly expressed in ACh interneurons and glutamatergic terminals, thereby regulating dopamine D2R function in the striatum (28).

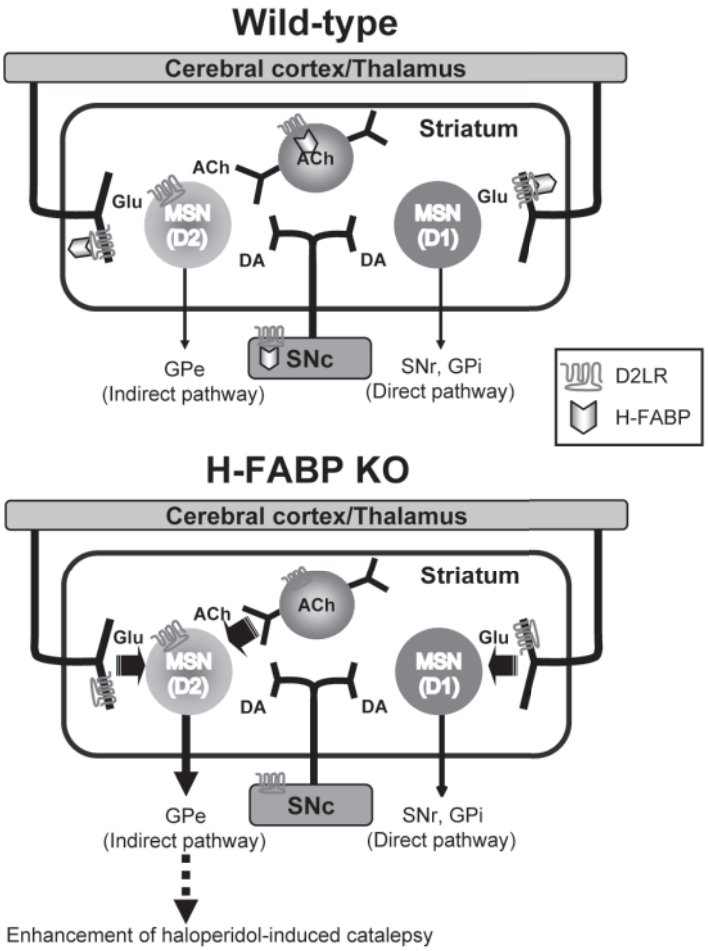

Fig. 2. Schematic representation summarizes changes in synaptic neurotransmission seen in the striatum microcircuit of H-FABP KO mice. Excitatory glutamatergic inputs to striatal neurons are derived from neurons in the cerebral cortex and thalamus. The target neurons include principal medium spiny neurons (MSNs) contributing to the direct pathway (D1R-expressing MSN) and the indirect pathway (D2R-expressing MSN). Striatonigral D1R-expressing MSNs directly project to the substantia nigra pars reticulata (SNr) and internal segment of the globus pallidus (GPi). By contrast, striatopallidal D2R-expressing MSNs project to the external segment of the globus pallidus (GPe). GPe neurons project to the subthalamic nucleus and then to the SNr and GPi. H-FABP binds to D2LR in acetylcholinergic interneurons and terminals of glutamatergic neurons, thereby regulating ACh and Glu release. H-FABP deletion causes D2R dysfunction and aberrantly increased ACh and Glu release is observed in H-FABP KO mice (Ref. 28). We propose that H-FABP KO mice exhibit increased excitability of striatopallidal MSNs through the aberrant increased ACh and Glu release, resulting in increased cataleptic responses.

5. Clinical relevance of FABPs in emotional and cognitive behaviors

Importantly, schizophrenic patients exhibit significantly lower levels in red blood cells of long chain polyunsaturated fatty acids (LCPUFAs), including arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (29). Several clinical studies indicate that oral administration of EPA can improve emotional and cognitive function in schizophrenic patients (30). Likewise, AA (31) and DHA (32) supplementation can improve cognitive dysfunction seen in human disorders such as Alzheimer's disease. Since LCPUFAs are insoluble in an aqueous cellular environment, FABPs are essential to function as cellular shuttles to transport LCPUFAs to appropriate intracellular compartments. Small 14 – 15-kDa cytoplasmic FABPs belong to a family consisting of at least 13 different widely distributed proteins. Among various FABPs, brain- (B-), epidermal- (E-), and heart- (H-) type FABPs are all expressed in the brain (33). B-FABP knockdown in cortical neuroepithelial cells by small interfering RNA impairs cell proliferation and promotes neuronal differentiation (34). B-FABP KO mice show abnormalities in emotional behavior, decreased neurogenesis in the dentate gyrus, and impaired prepulse inhibition (35). Given the phenotypes of B-FABP KO mice, the crucial roles of H-FABP in the D2LR signaling may explain the clinical relevance of LCPUFAs in ameliorating emotional and cognitive behaviors seen in schizophrenia and Alzheimer's diseases.

6. Conclusion

Notably, the activities of D2R/D3R are mediated not only by heterotrimeric G proteins but also by proteins interacting specifically with the third cytoplasmic loop. Interaction with NR2B, CaM, CaMKII, DAT, NFS, and Par-4 likely mediates synaptic plasticity related to memory and emotional behaviors. The functional relevance of other interacting proteins such as Filamin A and Protein 4.1N remains unclear. We have for the first time defined the physiological role of H-FABP interacting with the D2LR third cytoplasmic loop. Analysis of D2LR dysregulation in H-FABP KO mice should further our understanding of D2LR in METH-induced sensitization of locomotor and stereotypical behaviors through the nigrostriatal dopamine system.

References

1 Missale C, Nash R, Robinson SW, Jaber M, Caron MG. Dopamine receptors from structure to function. Physiol Rev. 1998; 78:189–225.

2 Sidhu A, Niznik HB. Coupling of dopamine receptor subtypes to multiple and diverse G proteins. Int J Dev Neurosci. 2000;18: 669–677.

3 Dal Toso R, Sommer B, Ewert M, Herb A, Pritchett DB, Bach A, et al. The dopamine D_2 receptor: two molecular forms generated by alternative splicing. EMBO J. 1989;8:4025–4034.

4 Itokawa M, Arinami T, Futamura N, Hamaguchi H, Toru M. A structural polymorphism of human dopamine D2 receptor, D2 (Ser311→Cys). Biochem Biophys Res. Commun. 1993;196: 1369–1375.

5 Arinami T, Itokawa M, Enguchi H, Tagaya H, Yano S, Shimizu H, et al. Association of dopamine D2 receptor molecular variant with schizophrenia. Lancet. 1994;343:703–704.

6 Laurent C, Bodeau-Pean S, Campion D, d'Amato T, Jay M, Dollfus S, et al. No major role for the dopamine D2 receptor Ser→Cys311 mutation in schizophrenia. Psychiatr Genet. 1994; 4:229–230.

7 Cravchik A, Sibley DR, Gejman PV. Functional analysis of the human D_2 dopamine receptor missense variants. J Biol Chem.1996;271:26013–26017.

8 Zhang Y, Bertolino A, Fazio L, Blasi G, Rampino A, Romano R, et al. Polymorphisms in human dopamine D2 receptor gene affect gene expression, splicing, and neuronal activity during working memory. Proc Natl Acad Sci U S A. 2007;104:20552–20557.

9 Richtand NM. Behavioral sensitization, alternative splicing, and d3 dopamine receptor-mediated inhibitory function. Neuropsychopharmacology. 2006;31:2368–2375.

10 Bofill-Cardona E, Kudlacek O, Yang Q, Ahorn H, Freissmuth M, Nanoff C. Binding of calmodulin to the D2-dopamine receptor reduces receptor signaling by arresting the G protein activation switch. J Biol Chem. 2000;275:32672–32680.

11 Rhoads AR, Friedberg F. Sequence motifs for calmodulin recognition. FASEB J. 1997;11:331–340.

12 Liu XY, Mao LM, Zhang GC, Papasian CJ, Fibuch EE, Lan HX, et al. Activity-dependent modulation of limbic dopamine D3 receptors by CaMKII. Neuron. 2009;61:425–438.

13 Collingridge GL, Singer W. Excitatory amino acid receptors and synaptic plasticity. Trends Pharmacol Sci. 1990;11:290–296.

14 Liu XY, Chu XP, Mao LM, Wang M, Lan HX, Li MH, et al. Modulation of D2R-NR2B interactions in response to cocaine. Neuron. 2006;52:897–909.

15 Ouimet CC, McGuinness TL, Greengard P. Immunocytochemical localization of calcium/calmodulin-dependent protein kinase II in rat brain. Proc Natl Acad Sci U S A. 1984;81:5604–5608.

16 Fukunaga K, Stoppini L, Miyamoto E, Muller D. Long-term potentiation is associated with a increased activity of Ca2+/calmodulin-dependent protein kinase II. J Biol Chem. 1993;268:7863–7867.

17 Lin R, Canfield V, Levenson R. Dominant negative mutants of filamin A block cell surface expression of the D2 dopamine receptor. Pharmacology. 2002;66:173–181.

18 Lin R, Karpa K, Kabbani N, Goldman-Rakic P, Levenson R. Dopamine D2 and D3 receptors are linked to the actin cytoskeleton via interaction with filamin A. Proc Natl Acad Sci U S A. 2001;98:5258–5263.

19 Walensky LD, Blackshaw S, Liao D, Watkins CC, Weier HU, Parra M, et al. A novel neuron-enriched homolog of the erythrocyte membrane cytoskeletal protein 4.1. J Neurosci. 1999;19:

6457–6467.
20 Binda AV, Kabbani N, Lin R, Levenson R. D2 and D3 dopamine receptor cell surface localization mediated by interaction with protein 4.1N. Mol Pharmacol. 2002;62:507–513.
21 Sells SF, Wood DP Jr, Joshi-Barve SS, Muthukumar S, Jacob RJ, Crist SA, et al. Commonality of the gene programs induced by effectors of apoptosis in androgen-dependent and -independent prostate cells. Cell Growth Differ. 1994;5:457–466.
22 Park SK, Nguyen MD, Fischer A, Luke MP, Affar el B, Dieffenbach PB, et al. Par-4 links dopamine signaling and depression. Cell. 2005;122:275–287.
23 Hanson PI, Otto H, Barton N, Jahn R. The N-ethylmaleimide-sensitive fusion protein and alpha-SNAP induce a conformational change in syntaxin. J Biol Chem. 1995;270:16955–16961.
24 Nishimune A, Isaac JT, Molnar E, Noel J, Nash SR, Tagaya M, et al. NSF binding to GluR2 regulates synaptic transmission. Neuron. 1998;21:87–97.
25 Zou S, Li L, Pei L, Vukusic B, Van Tol HH, Lee FJ, et al. Protein–protein coupling/uncoupling enables dopamine D2 receptor regulation of AMPA receptor-mediated excitotoxicity. J Neurosci. 2005;25:4385–4395.
26 Lee FJ, Pei L, Moszczynska A, Vukusic B, Fletcher PJ, Liu F. Dopamine transporter cell surface localization facilitated by a direct interaction with the dopamine D2 receptor. EMBO J. 2007;26:2127–2136.
27 Takeuchi Y, Fukunaga K. Differential subcellular localization of two dopamine D2 receptor isoforms in transfected NG108-15 cells. J Neurochem. 2003;85:1064–1074.
28 Shioda N, Yamamoto Y, Watanabe M, Binas B, Owada Y, Fukunaga K. Heart-type fatty acid binding protein regulates dopamine D2 receptor function in mouse brain. J Neurosci. 2010; 30:3146–3155.
29 Peet M, Laugharne J, Rangarajan N, Horrobin D, Reynolds G. Depleted red cell membrane essential fatty acids in drug-treated schizophrenic patients. J Psychiatr Res. 1995;29:227–232.
30 Arvindakshan M, Ghate M, Ranjekar PK, Evans DR, Mahadik SP. Supplementation with a combination of omega-3 fatty acids and antioxidants (vitamins E and C) improves the outcome of schizophrenia. Schizophr Res. 2003;62:195–204.
31 Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, et al. Dietary supplementation of arachidonic and docosahexaenoic acids improves cognitive dysfunction. Neurosci Res. 2006;56:159–164.
32 Horrocks LA, Yeo YK. Health benefits of docosahexaenoic acid (DHA). Pharmacol Res. 1999;40:211–225.
33 Owada Y, Yoshimoto T, Kondo H. Spatio-temporally differential expression of genes for three members of fatty acid-binding proteins in developing and mature rat brains. J Chem Neuroanat. 1996;12:113–122.
34 Arai Y, Funatsu N, Numayama-Tsuruta K, Nomura T, Nakamura S, Osumi N. Role of Fabp7, a downstream gene of Pax6, in the maintenance of neuroepithelial cells during early embryonic development of the rat cortex. J Neurosci. 2005;25:9752–9761.
35 Watanabe A, Toyota T, Owada Y, Hayashi T, Iwayama Y, Matsumata M, et al. Fabp7 maps to a quantitative trait locus for a schizophrenia endophenotype. PLoS Biol. 2007;5:e297.