Pathogenic Impact of FABP in Parkinson’s Disease

Subjects: Biology

Contributor: Ichiro Kawahata , Kohji Fukunaga

Parkinson’s disease is a neurodegenerative condition characterized by motor dysfunction resulting from the degeneration of dopamine-producing neurons in the midbrain. This dopamine deficiency gives rise to a spectrum of movement-related symptoms, including tremors, rigidity, and bradykinesia. While the precise etiology of Parkinson’s disease remains elusive, genetic mutations, protein aggregation, inflammatory processes, and oxidative stress are believed to contribute to its development. In this context, fatty acid-binding proteins (FABPs) in the central nervous system, FABP3, FABP5, and FABP7, impact α-synuclein aggregation, neurotoxicity, and neuroinflammation. These FABPs accumulate in mitochondria during neurodegeneration, disrupting their membrane potential and homeostasis. In particular, FABP3, abundant in nigrostriatal dopaminergic neurons, is responsible for α-synuclein propagation into neurons and intracellular accumulation, affecting the loss of mesencephalic tyrosine hydroxylase protein, a rate-limiting enzyme of dopamine biosynthesis.

Parkinson’s disease | tyrosine hydroxylase | dopaminergic neurons | fatty acid-binding protein | α-synuclein | mitochondria | dementia with Lewy bodies

1. Physiological Function of FABP and Involvement in Neurodegenerative Diseases

Fatty acids perform a variety of physiological functions in the body, serving as a source of energy for internal combustion, a major component of cell membranes, and a regulator of inflammatory responses. Excessive intake of fatty acids contributes to energy overload, obesity, and risk of brain inflammation. Fatty acids include saturated fatty acids; unsaturated fatty acids, which include monounsaturated and polyunsaturated fatty acids; and trans fatty acids. Some of these polyunsaturated fatty acids cannot be synthesized in the animal’s body and must be obtained from the diet. An excess of or deficiency in polyunsaturated fatty acids are associated with various functional disorders, neurological symptoms, and an increased risk of disease pathogenesis. Polyunsaturated fatty acids can be classified into omega-3 fatty acids, represented by docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), and omega-6 fatty acids, which are metabolized into linoleic acid and arachidonic acid.

Because fatty acids are hydrophobic, they require carrier proteins to transport them to intracellular organelles, and FABPs are responsible for this physiological function [1][2][3][4]. FABP is a protein consisting of approximately 130 amino acid residues, and nine isoforms have been identified in humans [5][6]. Each of these isoforms is known to have some specificity in its expression distribution (**Table 1**). Three of these isoforms, FABP3, FABP5, and FABP7,

are expressed in the nervous system [7][8][9][10]. FABP3, which was first identified in the heart [11][12], is abundantly expressed in mature neurons from the postnatal to the adult stage [9]. In contrast, FABP5 and FABP7 are maximally expressed in the fetus and neonate, during which time they are expressed in glial and neural stem cells [9][13][14]. FABP3 has a high affinity for n-6 polyunsaturated fatty acids such as arachidonic acid, FABP5 has a high affinity for saturated fatty acids such as stearic acid and palmitic acid, and FABP7 has a high affinity for n-3 polyunsaturated fatty acids such as DHA [15][16][17].

Polyunsaturated fatty acid itself affects the toxic expression of α-synuclein, the pathogenic protein of Parkinson's disease. Previous reports indicate that polyunsaturated fatty acids bind to α-synuclein and promote oligomer formation [18][19][20]. The exposure of cultured mesencephalic neurons to polyunsaturated fatty acids increased α-synuclein oligomer levels [20]. In addition, when mice expressing A53T, a representative mutant family line of α-synuclein in familial Parkinson's disease, were fed a DHA-containing diet, low concentrations of α-synuclein suppressed neuronal accumulation and toxic expression. In contrast, high concentrations of DHA increased intracellular accumulation of soluble and insoluble α-synuclein and neuronal injury [21]. In humans, fatty acids have also been implicated in the pathogenesis of Lewy body disease, and α-synuclein oligomers in the lipid fraction are detected in autopsy brains of Parkinson's disease and Lewy body dementia patients but not in healthy subjects [20]. Furthermore, a higher intake of arachidonic acid, an omega-6 polyunsaturated fatty acid, has been suggested to increase the risk of Parkinson's disease pathogenesis [22].

Furthermore, FABPs have pathogenic impacts and the potential for predictive biomarkers on various diseases, including brain injury and neurodegenerative disorders. FABP3 and FABP7 exhibit distinct distribution patterns within brain tissues, with FABP3 displaying notably higher concentrations in brain injury [23]. Elevated serum levels of FABP7 were observed in patients with Alzheimer's disease, Parkinson's disease, and other cognitive disorders [24]. In addition, FABP3 expression in the substantia nigra is known to be increased in autopsy brains of Parkinson's disease patients [25]. In this context, FABP3 co-localizes with phosphorylated α-synuclein in Lewy bodies [26]. Serum FABP3 levels are increased in patients with Parkinson's disease and dementia with Lewy bodies compared to healthy controls [27][28]. In addition, serum FABP3 was elevated in dementia with Lewy bodies and Parkinson's disease with dementia, compared to non-dementia controls [29][30]. These clinical findings suggest that FABP3 may be involved in the pathogenesis of Lewy body diseases, including Parkinson's disease. Based on these insights, the following chapters will describe the characteristics of Parkinson's disease, the selective degeneration of dopaminergic neurons, and the pathogenic impact of FABPs in the disease.

Table 1. Tissue distribution and expressed cell types of the fatty acid-binding protein (FABP) subfamilies.

FABP Subfamily	Tissue Distribution	Expressed Cells	Ref
FABP1 (Liver FABP)	Liver, intestine, kidney, pancreas	Hepatocytes, enterocytes	[31][32][33]
FABP2 (Intestinal	Intestine	Enterocytes	[34][35][36]

FABP Subfamily	Tissue Distribution	Expressed Cells	Ref
FABP)			
FABP3 (Heart FABP)	Heart, skeletal muscle, brain	Cardiomyocytes, myocytes, neurons	[13][37][38][39][40][41]
FABP4 (Adipocyte FABP)	Adipose tissue, macrophages	Adipocytes, macrophages	[42][43][44][45]
FABP5 (Epidermal FABP)	Epidermis, brain, adipose tissue	Keratinocytes, adipocytes, glial cells, neurons	[13][41][46][47][48]
FABP6 (Ileal FABP)	Intestine	Enterocytes	[49][50][51][52]
FABP7 (Brain FABP)	Brain, eye, kidney, mammary gland	Neural stem cells, oligodendrocytes, astrocytes, ependymal cells	[13][39][41][53][54]
FABP8 (Myelin FABP)	Myelin-forming cells in the peripheral nervous system	Schwann cells, oligodendrocytes	[41][54]
FABP9 (Testis FABP)	Testis	Salivary gland, mammary gland	[55][56]

2. Pathology of Parkinson's Disease and Current Issues

There are over 10 million Parkinson's disease patients worldwide, accounting for 1–3% of the global population aged 60 and above [57]. Half of those aged 85 and above develop Parkinson's disease [58]. The evolution of symptomatic therapies for Parkinson's disease, including dopamine agonists as well as L-DOPA, has been remarkable [59]. However, a fundamental treatment for Parkinson's disease has yet to be developed. Initiating treatment after onset does not lead to a favorable prognosis. At the onset of Parkinson's disease, the pathogenic proteins have already accumulated in the brain, and this pathology of dopaminergic neuronal loss induces clinical symptoms. Therefore, there is an expectation for the establishment of methods to predict the onset early.

Parkinson's disease was first diagnosed by James Parkinson in 1817, detailing its clinical features as tremor, rigidity, bradykinesia, gait disturbances, and postural instability [60]. Cognitive symptoms commonly emerge in the advanced stages of the disease [61]. Approximately 20–40% of all Parkinson's cases develop Parkinson's disease dementia, with an average progression time of 10 years. In total, 40% of Parkinson's patients with severe olfactory dysfunction progress to dementia [62][63]. In this regard, the importance of the olfactory bulb as an entry site for prion-like transmission in neurodegenerative diseases is suggested [64]. Pathologically, Parkinson's disease is characterized by the loss of dopamine-biosynthesizing neurons in the substantia nigra pars compacta. It is also denoted by the abnormal deposition of the pathogenic protein α-synuclein in the cell body and neuronal processes, forming Lewy bodies and Lewy neurites, respectively [65][66][67]. Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies share the accumulation and aggregation of the pathogenic protein α-

synuclein within neurons, leading to the formation of Lewy bodies. Therefore, these Lewy body diseases are believed to share common pathological mechanisms.

The decline in motor function observed in Parkinson's disease arises due to impaired nigrostriatal dopaminergic function [68]. Nigrostriatal dopaminergic projections centrally regulate voluntary movements, and their degeneration contributes to Parkinsonian clinical symptoms. In addition, the dopaminergic system, originating in the substantia nigra pars compacta and the ventral tegmental area, predominantly projecting to the striatum and prefrontal context, significantly influences behavioral activities [69][70][71]. Consequently, lesions in nigral neurons cause concurrent dysfunction of agonist and antagonist muscle pairs in animal models of Parkinsonism [72] and sporadic Parkinson's disease [73]. The dopaminergic function is regulated by the neurotransmitter dopamine. This catecholamine is biosynthesized from L-tyrosine by the rate-limiting enzyme tyrosine hydroxylase (TH) and aromatic L-amino acid decarboxylase (AADC) [74]. TH requires tetrahydrobiopterin, which is biosynthesized by GTP cyclohydrolase I (GTPCH1), to perform its enzymatic activity [75][76]. Because the enzymatic activity of TH protein strictly controls the rate-limiting step of dopamine biosynthesis [77], unlike those of other dopamine biosynthesizing enzymes, the expression level and activity of TH, which is precisely regulated via phosphorylation, directly affect intracellular dopamine amount.

3. Therapeutic Potential of FABP-Targeting Drugs for Parkinson's Disease

As previously mentioned, the presence of FABPs is closely related to the maintenance of dopaminergic homeostasis and mitochondrial function in neurodegeneration. FABP3 and FABP5 are essential for the neurotoxicity expression of α-synuclein. Considering the potential for drug development targeting FABP3, researchers observed the absence of α-synuclein neurotoxicity in genetic knockout cells of FABP3. It was found that FABP3 can bind to α-synuclein in a 1:1 ratio, promoting α-synuclein-FABP3 aggregate formation [78]. Consequently, researchers attempted to create a drug that could inhibit the interaction between FABP3 and α-synuclein [79][80].

The FABP3 ligand, as a targeted drug for FABP3, inhibits α-synuclein aggregation and prevents its propagation in the brain and subsequent neuronal loss [81]. The FABP3 ligand effectively prevents the degeneration of dopaminergic neurons and restores motor dysfunction to a healthy level in a Parkinson's disease mouse model [79]. Additionally, an α-synuclein mimicking peptide that inhibits the binding and aggregate formation of α-synuclein-FABP3 is capable of restoring memory and learning abilities in a Parkinson's disease dementia mouse model [80]. This peptide has the potential to alleviate α-synuclein phosphorylation, which links to neurotoxicity. Researchers are currently conducting preclinical trials of small molecules targeting FABP3 (Japan Agency for Medical Research and Development (AMED), Translational Research Program 23ym0126095h0002).

With regard to FABP5, the specific ligand for FABP5 abolishes α-synuclein accumulation and translocation to mitochondria, which alleviates neurotoxicity in Parkinson's disease model neuronal cells [82], as well as ameliorates oligodendrocyte injury in multiple sclerosis mouse models [83] and psychosine-induced apoptosis in Krabbe disease

models [84]. Furthermore, the FABP5 ligand also has the ability to ameliorate FABP3/5-induced mitochondrial injury, including lipid peroxidation and BAX-related apoptotic signaling, indicating the potential neuroprotective treatment for ischemic stroke [85][86]. In addition, regarding FABP7, the ligand alleviates FABP7-induced α-synuclein oligomerization and aggregation, thereby rescuing glial and oligodendrocytes from cell death in multiple system atrophy model cells and mice [87][88][89]. These data suggest the promising potential of unique drug developments targeting FABP to regulate dopaminergic signaling and protect neuronal homeostasis.

4. Diagnostic Potential of FABPs as a Prodromal Biomarker for Parkinson's Diseases

In recent years, there has been remarkable progress in targeted therapy for Parkinson's disease, allowing for the precise alleviation of clinical symptoms [90][91]. However, challenges remain that affect the quality of life for patients, including subcutaneous device attachment, reduced medication efficacy due to disease progression, and the presence of OFF symptoms. In neurodegenerative diseases, post-onset treatment does not yield favorable prognoses, making fundamental treatment challenging. To overcome Parkinson's disease, it is necessary to predict disease risk before onset and achieve early therapeutic interventions. Numerous excellent studies have been reported on diagnostic techniques for Parkinson's disease using analyses of cerebrospinal fluid (CSF), serum, and plasma biomarkers targeting α-synuclein and other related proteins [92][93][94][95]. Additionally, recent studies have demonstrated that severe olfactory impairment is a useful early biomarker for Parkinson's disease dementia [62][63][96][97][98].

Previously, certain reports have suggested methods to predict Parkinson's disease using FABP3 as a biomarker in the cerebrospinal fluid or serum [29][30][99][100][101][102][103][104]. These investigations spotlight the pathogenic significance of the cerebrospinal fluid and serum FABP3 levels, indicating characteristic modifications in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies. Elevated FABP3 levels are invariably observed in cerebrospinal fluid and serum specimens from patients with these disorders. Notably, higher FABP3 levels are observed in patients with dementia with Lewy bodies than in Parkinson's disease dementia and Alzheimer's disease, indicating the potential of FABP3 as a biomarker distinctive to dementia with Lewy bodies.

Therefore, with the aim of establishing a more accurate technique using plasma biomarkers to predict disease risk and discriminate potential disease types, researchers recently focused on FABP family proteins, essential for the propagation and expression of α-synuclein neurotoxicity, and developed a differential diagnostic technique for neurodegenerative disorders through a multi-marker analysis in combination with known biomarkers [28]. This method not only allows the discrimination between healthy individuals and those with Parkinson's disease but also enables the prediction of Lewy body dementia, Alzheimer's disease, and mild cognitive impairment. Specifically, researchers established a scoring technique that can differentiate Parkinson's disease, Lewy body dementia, and Alzheimer's disease from healthy individuals and also can distinguish between different neurodegenerative diseases (**Figure 1**) [28]. These multi-marker disease risk scores correlate with clinical symptoms in each disease, specifically mini-mental state examination (MMSE) scores and Hoehn–Yahr stages in Parkinson's disease. The

researchers hope that this technology will contribute to the differentiation of clinically challenging conditions such as Parkinson's disease dementia, Lewy body dementia, and Alzheimer's disease in clinical settings.

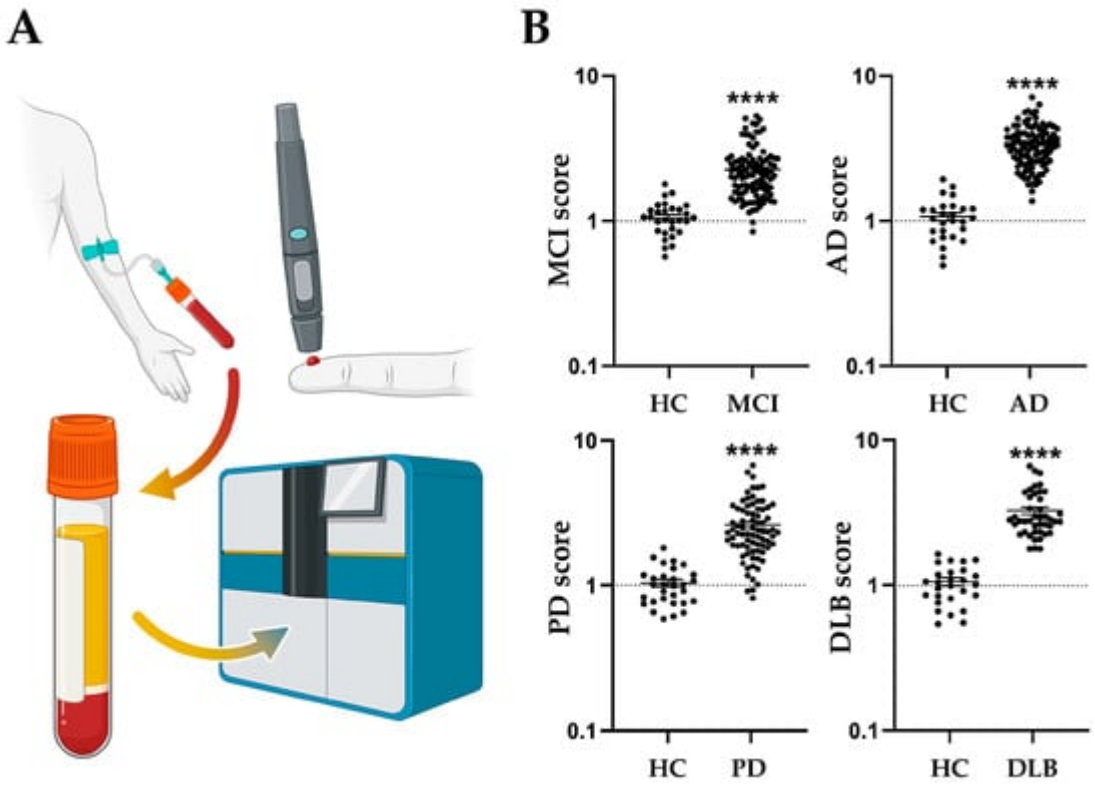

Figure 1. Technique for quantifying risk scores for neurodegenerative diseases using plasma biomarkers. (**A**) Flow chart from blood collection to plasma preparation and ELISA analysis. In addition to blood collection at the hospital, patients or healthy ones can collect their own blood at home. Plasma samples are analyzed using high-sensitivity immunoassays [28]. (**B**) Representative quantified data of risk scores for mild cognitive impairment (MCI), Alzheimer's disease (AD), Parkinson's disease (PD), and dementia with Lewy bodies (DLB) [28]. Student's t-test is used to compare the means between each group. **** $p < 0.0001$ versus healthy controls (HC).

In addition to ELISA analysis, metabolomics is a useful tool for measuring biomarkers [105][106]. ELISA analysis of plasma can measure the amount of a specific protein. This method is considered very accurate and reliable when the protein to be measured is known. Therefore, understanding the pathogenetic significance of the target proteins is essential. In contrast, metabolomics analysis, on the other hand, provides a comprehensive measurement of metabolites in vivo. The advantage of this method is that measurement is possible even if the metabolite to be measured is unknown. In this respect, compared to ELISA analysis, it may require more advanced techniques to account for measurement accuracy. Previous metabolomics studies successfully revealed lipid dysregulation in Parkinson's disease [107][108]. Through utilizing the advantages of both of these approaches and establishing more accurate and highly specific biomarker predictions, it would be possible to produce a very early diagnosis of Parkinson's disease before its onset.

References

1. Ockner, R.K.; Manning, J.A.; Poppenhausen, R.B.; Ho, W.K. A binding protein for fatty acids in cytosol of intestinal mucosa, liver, myocardium, and other tissues. Science 1972, 177, 56–58.
2. Veerkamp, J.H. Fatty acid transport and fatty acid-binding proteins. Proc. Nutr. Soc. 1995, 54, 23–37.
3. Coe, N.R.; Bernlohr, D.A. Physiological properties and functions of intracellular fatty acid-binding proteins. Biochim. Biophys. Acta 1998, 1391, 287–306.
4. Storch, J.; Thumser, A.E. The fatty acid transport function of fatty acid-binding proteins. Biochim. Biophys. Acta 2000, 1486, 28–44.
5. Chmurzyńska, A. The multigene family of fatty acid-binding proteins (FABPs): Function, structure and polymorphism. J. Appl. Genet. 2006, 47, 39–48.
6. Smathers, R.L.; Petersen, D.R. The human fatty acid-binding protein family: Evolutionary divergences and functions. Hum. Genom. 2011, 5, 170–191.
7. Zimmerman, A.W.; Veerkamp, J.H. New insights into the structure and function of fatty acid-binding proteins. Cell. Mol. Life Sci. 2002, 59, 1096–1116.
8. Zimmerman, A.W.; van Moerkerk, H.T.; Veerkamp, J.H. Ligand specificity and conformational stability of human fatty acid-binding proteins. Int. J. Biochem. Cell Biol. 2001, 33, 865–876.
9. Liu, R.Z.; Mita, R.; Beaulieu, M.; Gao, Z.; Godbout, R. Fatty acid binding proteins in brain development and disease. Int. J. Dev. Biol. 2010, 54, 1229–1239.
10. Xu, B.; Chen, L.; Zhan, Y.; Marquez, K.N.S.; Zhuo, L.; Qi, S.; Zhu, J.; He, Y.; Chen, X.; Zhang, H.; et al. The Biological Functions and Regulatory Mechanisms of Fatty Acid Binding Protein 5 in Various Diseases. Front. Cell Dev. Biol. 2022, 10, 857919.
11. Binas, B.; Danneberg, H.; McWhir, J.; Mullins, L.; Clark, A.J. Requirement for the heart-type fatty acid binding protein in cardiac fatty acid utilization. FASEB J. 1999, 13, 805–812.
12. Schaap, F.G.; Binas, B.; Danneberg, H.; van der Vusse, G.J.; Glatz, J.F. Impaired long-chain fatty acid utilization by cardiac myocytes isolated from mice lacking the heart-type fatty acid binding protein gene. Circ. Res. 1999, 85, 329–337.
13. 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.
14. Owada, Y. Fatty acid binding protein: Localization and functional significance in the brain. Tohoku J. Exp. Med. 2008, 214, 213–220.

15. Hanhoff, T.; Lucke, C.; Spener, F. Insights into binding of fatty acids by fatty acid binding proteins. Mol. Cell. Biochem. 2002, 239, 45–54.
16. Armstrong, E.H.; Goswami, D.; Griffin, P.R.; Noy, N.; Ortlund, E.A. Structural basis for ligand regulation of the fatty acid-binding protein 5, peroxisome proliferator-activated receptor beta/delta (FABP5-PPARbeta/delta) signaling pathway. J. Biol. Chem. 2014, 289, 14941–14954.
17. Mita, R.; Beaulieu, M.J.; Field, C.; Godbout, R. Brain fatty acid-binding protein and omega-3/omega-6 fatty acids: Mechanistic insight into malignant glioma cell migration. J. Biol. Chem. 2010, 285, 37005–37015.
18. Perrin, R.J.; Woods, W.S.; Clayton, D.F.; George, J.M. Exposure to long chain polyunsaturated fatty acids triggers rapid multimerization of synucleins. J. Biol. Chem. 2001, 276, 41958–41962.
19. Sharon, R.; Goldberg, M.S.; Bar-Josef, I.; Betensky, R.A.; Shen, J.; Selkoe, D.J. alpha-Synuclein occurs in lipid-rich high molecular weight complexes, binds fatty acids, and shows homology to the fatty acid-binding proteins. Proc. Natl. Acad. Sci. USA 2001, 98, 9110–9115.
20. Sharon, R.; Bar-Joseph, I.; Frosch, M.P.; Walsh, D.M.; Hamilton, J.A.; Selkoe, D.J. The formation of highly soluble oligomers of alpha-synuclein is regulated by fatty acids and enhanced in Parkinson’s disease. Neuron 2003, 37, 583–595.
21. Yakunin, E.; Loeb, V.; Kisos, H.; Biala, Y.; Yehuda, S.; Yaari, Y.; Selkoe, D.J.; Sharon, R. Alpha-synuclein neuropathology is controlled by nuclear hormone receptors and enhanced by docosahexaenoic acid in a mouse model for Parkinson’s disease. Brain Pathol. 2012, 22, 280–294.
22. Miyake, Y.; Sasaki, S.; Tanaka, K.; Fukushima, W.; Kiyohara, C.; Tsuboi, Y.; Yamada, T.; Oeda, T.; Miki, T.; Kawamura, N.; et al. Dietary fat intake and risk of Parkinson’s disease: A case-control study in Japan. J. Neurol. Sci. 2010, 288, 117–122.
23. Pelsers, M.M.; Hanhoff, T.; Van der Voort, D.; Arts, B.; Peters, M.; Ponds, R.; Honig, A.; Rudzinski, W.; Spener, F.; de Kruijk, J.R.; et al. Brain- and heart-type fatty acid-binding proteins in the brain: Tissue distribution and clinical utility. Clin. Chem. 2004, 50, 1568–1575.
24. Teunissen, C.E.; Veerhuis, R.; De Vente, J.; Verhey, F.R.; Vreeling, F.; van Boxtel, M.P.; Glatz, J.F.; Pelsers, M.A. Brain-specific fatty acid-binding protein is elevated in serum of patients with dementia-related diseases. Eur. J. Neurol. 2011, 18, 865–871.
25. Basso, M.; Giraudo, S.; Corpillo, D.; Bergamasco, B.; Lopiano, L.; Fasano, M. Proteome analysis of human substantia nigra in Parkinson’s disease. Proteomics 2004, 4, 3943–3952.
26. Oizumi, H.; Yamasaki, K.; Suzuki, H.; Hasegawa, T.; Sugimura, Y.; Baba, T.; Fukunaga, K.; Takeda, A. Fatty Acid-Binding Protein 3 Expression in the Brain and Skin in Human Synucleinopathies. Front. Aging Neurosci. 2021, 13, 648982.

27. Wada-Isoe, K.; Imamura, K.; Kitamaya, M.; Kowa, H.; Nakashima, K. Serum heart-fatty acid binding protein levels in patients with Lewy body disease. J. Neurol. Sci. 2008, 266, 20–24.
28. Kawahata, I.; Sekimori, T.; Oizumi, H.; Takeda, A.; Fukunaga, K. Using Fatty Acid-Binding Proteins as Potential Biomarkers to Discriminate between Parkinson’s Disease and Dementia with Lewy Bodies: Exploration of a Novel Technique. Int. J. Mol. Sci. 2023, 24, 13267.
29. Mollenhauer, B.; Steinacker, P.; Bahn, E.; Bibl, M.; Brechlin, P.; Schlossmacher, M.G.; Locascio, J.J.; Wiltfang, J.; Kretzschmar, H.A.; Poser, S.; et al. Serum heart-type fatty acid-binding protein and cerebrospinal fluid tau: Marker candidates for dementia with Lewy bodies. Neurodegener. Dis. 2007, 4, 366–375.
30. Backstrom, D.C.; Eriksson Domellof, M.; Linder, J.; Olsson, B.; Ohrfelt, A.; Trupp, M.; Zetterberg, H.; Blennow, K.; Forsgren, L. Cerebrospinal Fluid Patterns and the Risk of Future Dementia in Early, Incident Parkinson Disease. JAMA Neurol. 2015, 72, 1175–1182.
31. Ockner, R.K.; Manning, J.A.; Kane, J.P. Fatty acid binding protein. Isolation from rat liver, characterization, and immunochemical quantification. J. Biol. Chem. 1982, 257, 7872–7878.
32. Lowe, J.B.; Boguski, M.S.; Sweetser, D.A.; Elshourbagy, N.A.; Taylor, J.M.; Gordon, J.I. Human liver fatty acid binding protein. Isolation of a full length cDNA and comparative sequence analyses of orthologous and paralogous proteins. J. Biol. Chem. 1985, 260, 3413–3417.
33. Sweetser, D.A.; Lowe, J.B.; Gordon, J.I. The nucleotide sequence of the rat liver fatty acid-binding protein gene. Evidence that exon 1 encodes an oligopeptide domain shared by a family of proteins which bind hydrophobic ligands. J. Biol. Chem. 1986, 261, 5553–5561.
34. Alpers, D.H.; Strauss, A.W.; Ockner, R.K.; Bass, N.M.; Gordon, J.I. Cloning of a cDNA encoding rat intestinal fatty acid binding protein. Proc. Natl. Acad. Sci. USA 1984, 81, 313–317.
35. Sweetser, D.A.; Birkenmeier, E.H.; Klisak, I.J.; Zollman, S.; Sparkes, R.S.; Mohandas, T.; Lusis, A.J.; Gordon, J.I. The human and rodent intestinal fatty acid binding protein genes. A comparative analysis of their structure, expression, and linkage relationships. J. Biol. Chem. 1987, 262, 16060–16071.
36. Green, R.P.; Cohn, S.M.; Sacchettini, J.C.; Jackson, K.E.; Gordon, J.I. The mouse intestinal fatty acid binding protein gene: Nucleotide sequence, pattern of developmental and regional expression, and proposed structure of its protein product. DNA Cell Biol. 1992, 11, 31–41.
37. Sacchettini, J.C.; Said, B.; Schulz, H.; Gordon, J.I. Rat heart fatty acid-binding protein is highly homologous to the murine adipocyte 422 protein and the P2 protein of peripheral nerve myelin. J. Biol. Chem. 1986, 261, 8218–8223.
38. Heuckeroth, R.O.; Birkenmeier, E.H.; Levin, M.S.; Gordon, J.I. Analysis of the tissue-specific expression, developmental regulation, and linkage relationships of a rodent gene encoding heart fatty acid binding protein. J. Biol. Chem. 1987, 262, 9709–9717.

39. Kurtz, A.; Zimmer, A.; Schnütgen, F.; Brüning, G.; Spener, F.; Müller, T. The expression pattern of a novel gene encoding brain-fatty acid binding protein correlates with neuronal and glial cell development. Development 1994, 120, 2637–2649.

40. Sellner, P.A.; Chu, W.; Glatz, J.F.; Berman, N.E. Developmental role of fatty acid-binding proteins in mouse brain. Brain Res. Dev. Brain Res. 1995, 89, 33–46.

41. Veerkamp, J.H.; Zimmerman, A.W. Fatty acid-binding proteins of nervous tissue. J. Mol. Neurosci. 2001, 16, 133–142; discussion 151–157.

42. Spiegelman, B.M.; Frank, M.; Green, H. Molecular cloning of mRNA from 3T3 adipocytes. Regulation of mRNA content for glycerophosphate dehydrogenase and other differentiation-dependent proteins during adipocyte development. J. Biol. Chem. 1983, 258, 10083–10089.

43. Bernlohr, D.A.; Angus, C.W.; Lane, M.D.; Bolanowski, M.A.; Kelly, T.J., Jr. Expression of specific mRNAs during adipose differentiation: Identification of an mRNA encoding a homologue of myelin P2 protein. Proc. Natl. Acad. Sci. USA 1984, 81, 5468–5472.

44. Amri, E.Z.; Bertrand, B.; Ailhaud, G.; Grimaldi, P. Regulation of adipose cell differentiation. I. Fatty acids are inducers of the aP2 gene expression. J. Lipid Res. 1991, 32, 1449–1456.

45. Bernlohr, D.A.; Coe, N.R.; Simpson, M.A.; Hertzel, A.V. Regulation of gene expression in adipose cells by polyunsaturated fatty acids. Adv. Exp. Med. Biol. 1997, 422, 145–156.

46. Madsen, P.; Rasmussen, H.H.; Leffers, H.; Honoré, B.; Celis, J.E. Molecular cloning and expression of a novel keratinocyte protein (psoriasis-associated fatty acid-binding protein) that is highly up-regulated in psoriatic skin and that shares similarity to fatty acid-binding proteins. J. Investig. Dermatol. 1992, 99, 299–305.

47. Krieg, P.; Feil, S.; Fürstenberger, G.; Bowden, G.T. Tumor-specific overexpression of a novel keratinocyte lipid-binding protein. Identification and characterization of a cloned sequence activated during multistage carcinogenesis in mouse skin. J. Biol. Chem. 1993, 268, 17362–17369.

48. Liu, Y.; Longo, L.D.; De Leon, M. In situ and immunocytochemical localization of E-FABP mRNA and protein during neuronal migration and differentiation in the rat brain. Brain Res. 2000, 852, 16–27.

49. Gong, Y.Z.; Everett, E.T.; Schwartz, D.A.; Norris, J.S.; Wilson, F.A. Molecular cloning, tissue distribution, and expression of a 14-kDa bile acid-binding protein from rat ileal cytosol. Proc. Natl. Acad. Sci. USA 1994, 91, 4741–4745.

50. Vodenlich, A.D., Jr.; Gong, Y.Z.; Geoghegan, K.F.; Lin, M.C.; Lanzetti, A.J.; Wilson, F.A. Identification of the 14 kDa bile acid transport protein of rat ileal cytosol as gastrotropin. Biochem. Biophys. Res. Commun. 1991, 177, 1147–1154.

51. Walz, D.A.; Wider, M.D.; Snow, J.W.; Dass, C.; Desiderio, D.M. The complete amino acid sequence of porcine gastrotropin, an ileal protein which stimulates gastric acid and pepsinogen secretion. J. Biol. Chem. 1988, 263, 14189–14195.
52. Gantz, I.; Nothwehr, S.F.; Lucey, M.; Sacchettini, J.C.; DelValle, J.; Banaszak, L.J.; Naud, M.; Gordon, J.I.; Yamada, T. Gastrotropin: Not an enterooxyntin but a member of a family of cytoplasmic hydrophobic ligand binding proteins. J. Biol. Chem. 1989, 264, 20248–20254.
53. Feng, L.; Hatten, M.E.; Heintz, N. Brain lipid-binding protein (BLBP): A novel signaling system in the developing mammalian CNS. Neuron 1994, 12, 895–908.
54. Shimizu, F.; Watanabe, T.K.; Shinomiya, H.; Nakamura, Y.; Fujiwara, T. Isolation and expression of a cDNA for human brain fatty acid-binding protein (B-FABP). Biochim. Biophys. Acta 1997, 1354, 24–28.
55. Oko, R.; Morales, C.R. A novel testicular protein, with sequence similarities to a family of lipid binding proteins, is a major component of the rat sperm perinuclear theca. Dev. Biol. 1994, 166, 235–245.
56. Pouresmaeili, F.; Morales, C.R.; Oko, R. Molecular cloning and structural analysis of the gene encoding PERF 15 protein present in the perinuclear theca of the rat spermatozoa. Biol. Reprod. 1997, 57, 655–659.
57. de Lau, L.M.; Breteler, M.M. Epidemiology of Parkinson’s disease. Lancet Neurol. 2006, 5, 525–535.
58. Hirsch, L.; Jette, N.; Frolkis, A.; Steeves, T.; Pringsheim, T. The Incidence of Parkinson’s Disease: A Systematic Review and Meta-Analysis. Neuroepidemiology 2016, 46, 292–300.
59. Ruan, X.; Lin, F.; Wu, D.; Chen, L.; Weng, H.; Yu, J.; Wang, Y.; Chen, Y.; Chen, X.; Ye, Q.; et al. Comparative Efficacy and Safety of Dopamine Agonists in Advanced Parkinson’s Disease With Motor Fluctuations: A Systematic Review and Network Meta-Analysis of Double-Blind Randomized Controlled Trials. Front. Neurosci. 2021, 15, 728083.
60. Parkinson, J. An essay on the shaking palsy. 1817. J. Neuropsychiatry Clin. Neurosci. 2002, 14, 223–236; discussion 222.
61. Phillips, O.; Ghosh, D.; Fernandez, H.H. Parkinson Disease Dementia Management: An Update of Current Evidence and Future Directions. Curr. Treat. Options Neurol. 2023, 25, 93–119.
62. Takeda, A.; Baba, T.; Kikuchi, A.; Hasegawa, T.; Sugeno, N.; Konno, M.; Miura, E.; Mori, E. Olfactory dysfunction and dementia in Parkinson’s disease. J. Park. Dis. 2014, 4, 181–187.
63. Takeda, A. How Useful is an Olfactory Test for Diagnosing Alzheimer’s Syndrome? Brain Nerve 2023, 75, 943–948.

64. Rey, N.L.; Wesson, D.W.; Brundin, P. The olfactory bulb as the entry site for prion-like propagation in neurodegenerative diseases. Neurobiol. Dis. 2018, 109, 226–248.
65. Spillantini, M.G.; Schmidt, M.L.; Lee, V.M.; Trojanowski, J.Q.; Jakes, R.; Goedert, M. Alpha-synuclein in Lewy bodies. Nature 1997, 388, 839–840.
66. Spillantini, M.G.; Crowther, R.A.; Jakes, R.; Hasegawa, M.; Goedert, M. alpha-Synuclein in filamentous inclusions of Lewy bodies from Parkinson’s disease and dementia with lewy bodies. Proc. Natl. Acad. Sci. USA 1998, 95, 6469–6473.
67. Spillantini, M.G.; Crowther, R.A.; Jakes, R.; Cairns, N.J.; Lantos, P.L.; Goedert, M. Filamentous alpha-synuclein inclusions link multiple system atrophy with Parkinson’s disease and dementia with Lewy bodies. Neurosci. Lett. 1998, 251, 205–208.
68. Shetty, A.S.; Bhatia, K.P.; Lang, A.E. Dystonia and Parkinson’s disease: What is the relationship? Neurobiol. Dis. 2019, 132, 104462.
69. Montague, P.R.; Hyman, S.E.; Cohen, J.D. Computational roles for dopamine in behavioural control. Nature 2004, 431, 760–767.
70. Schultz, W. Behavioral theories and the neurophysiology of reward. Annu. Rev. Psychol. 2006, 57, 87–115.
71. Berridge, K.C. From prediction error to incentive salience: Mesolimbic computation of reward motivation. Eur. J. Neurosci. 2012, 35, 1124–1143.
72. Stern, G. The effects of lesions in the substantia nigra. Brain 1966, 89, 449–478.
73. Hoefer, P.F.A. Action Potentials of Muscles in Rigidity and Tremor. Arch. Neurol. Psychiatry 1940, 43, 704–725.
74. Nagatsu, T. The catecholamine system in health and disease -Relation to tyrosine 3-monooxygenase and other catecholamine-synthesizing enzymes. Proc. Jpn. Acad. Ser. B Phys. Biol. Sci. 2007, 82, 388–415.
75. Nagatsu, T.; Nagatsu, I. Tyrosine hydroxylase (TH), its cofactor tetrahydrobiopterin (BH4), other catecholamine-related enzymes, and their human genes in relation to the drug and gene therapies of Parkinson’s disease (PD): Historical overview and future prospects. J. Neural Transm. 2016, 123, 1255–1278.
76. Nagatsu, T. Catecholamines and Parkinson’s disease: Tyrosine hydroxylase (TH) over tetrahydrobiopterin (BH4) and GTP cyclohydrolase I (GCH1) to cytokines, neuromelanin, and gene therapy: A historical overview. J. Neural Transm. 2023. ahead of print.
77. Nagatsu, T.; Levitt, M.; Udenfriend, S. Tyrosine Hydroxylase. The initial step in norepinephrine biosynthesis. J. Biol. Chem. 1964, 239, 2910–2917.

78. Fukui, N.; Yamamoto, H.; Miyabe, M.; Aoyama, Y.; Hongo, K.; Mizobata, T.; Kawahata, I.; Yabuki, Y.; Shinoda, Y.; Fukunaga, K.; et al. An alpha-synuclein decoy peptide prevents cytotoxic alpha-synuclein aggregation caused by fatty acid binding protein 3. J. Biol. Chem. 2021, 296, 100663.
79. Wang, H.; Fukunaga, K.; Cheng, A.; Wang, Y.; Arimura, N.; Yoshino, H.; Sasaki, T.; Kawahata, I. Novel FABP3 ligand, HY-11-9, ameliorates neuropathological deficits in MPTP-induced Parkinsonism in mice. J. Pharmacol. Sci. 2023, 152, 30–38.
80. Guo, Q.; Kawahata, I.; Jia, W.; Wang, H.; Cheng, A.; Yabuki, Y.; Shioda, N.; Fukunaga, K. alpha-Synuclein decoy peptide protects mice against alpha-synuclein-induced memory loss. CNS Neurosci. Ther. 2023, 29, 1547–1560.
81. Yabuki, Y.; Matsuo, K.; Kawahata, I.; Fukui, N.; Mizobata, T.; Kawata, Y.; Owada, Y.; Shioda, N.; Fukunaga, K. Fatty Acid Binding Protein 3 Enhances the Spreading and Toxicity of alpha-Synuclein in Mouse Brain. Int. J. Mol. Sci. 2020, 21, 2230.
82. Wang, Y.; Shinoda, Y.; Cheng, A.; Kawahata, I.; Fukunaga, K. Epidermal Fatty Acid-Binding Protein 5 (FABP5) Involvement in Alpha-Synuclein-Induced Mitochondrial Injury under Oxidative Stress. Biomedicines 2021, 9, 110.
83. Cheng, A.; Jia, W.; Kawahata, I.; Fukunaga, K. A novel fatty acid-binding protein 5 and 7 inhibitor ameliorates oligodendrocyte injury in multiple sclerosis mouse models. EBioMedicine 2021, 72, 103582.
84. Cheng, A.; Kawahata, I.; Fukunaga, K. Fatty Acid Binding Protein 5 Mediates Cell Death by Psychosine Exposure through Mitochondrial Macropores Formation in Oligodendrocytes. Biomedicines 2020, 8, 635.
85. Guo, Q.; Kawahata, I.; Degawa, T.; Ikeda-Matsuo, Y.; Sun, M.; Han, F.; Fukunaga, K. Fatty Acid-Binding Proteins Aggravate Cerebral Ischemia-Reperfusion Injury in Mice. Biomedicines 2021, 9, 529.
86. Guo, Q.; Kawahata, I.; Cheng, A.; Wang, H.; Jia, W.; Yoshino, H.; Fukunaga, K. Fatty acid-binding proteins 3 and 5 are involved in the initiation of mitochondrial damage in ischemic neurons. Redox Biol. 2023, 59, 102547.
87. Cheng, A.; Wang, Y.F.; Shinoda, Y.; Kawahata, I.; Yamamoto, T.; Jia, W.B.; Yamamoto, H.; Mizobata, T.; Kawata, Y.; Fukunaga, K. Fatty acid-binding protein 7 triggers alpha-synuclein oligomerization in glial cells and oligodendrocytes associated with oxidative stress. Acta Pharmacol. Sin. 2022, 43, 552–562.
88. Cheng, A.; Kawahata, I.; Wang, Y.; Jia, W.; Wang, H.; Sekimori, T.; Chen, Y.; Suzuki, H.; Takeda, A.; Stefanova, N.; et al. Epsin2, a novel target for multiple system atrophy therapy via alpha-synuclein/FABP7 propagation. Brain 2023, 146, 3172–3180.

89. Cheng, A.; Jia, W.; Finkelstein, D.I.; Stefanova, N.; Wang, H.; Sasaki, T.; Kawahata, I.; Fukunaga, K. Pharmacological inhibition of FABP7 by MF 6 counteracts cerebellum dysfunction in an experimental multiple system atrophy mouse model. Acta Pharmacol. Sin. 2023. ahead of print.
90. Ntetsika, T.; Papathoma, P.E.; Markaki, I. Novel targeted therapies for Parkinson’s disease. Mol. Med. 2021, 27, 17.
91. Prasad, E.M.; Hung, S.Y. Current Therapies in Clinical Trials of Parkinson’s Disease: A 2021 Update. Pharmaceuticals 2021, 14, 717.
92. Mollenhauer, B.; Cullen, V.; Kahn, I.; Krastins, B.; Outeiro, T.F.; Pepivani, I.; Ng, J.; Schulz-Schaeffer, W.; Kretzschmar, H.A.; McLean, P.J.; et al. Direct quantification of CSF alpha-synuclein by ELISA and first cross-sectional study in patients with neurodegeneration. Exp. Neurol. 2008, 213, 315–325.
93. Li, X.; Fan, X.; Yang, H.; Liu, Y. Review of Metabolomics-Based Biomarker Research for Parkinson’s Disease. Mol. Neurobiol. 2022, 59, 1041–1057.
94. Ma, Z.L.; Wang, Z.L.; Zhang, F.Y.; Liu, H.X.; Mao, L.H.; Yuan, L. Biomarkers of Parkinson’s Disease: From Basic Research to Clinical Practice. Aging Dis. 2023. ahead of print.
95. Tsamourgelis, A.; Swann, P.; Chouliaras, L.; O’Brien, J.T. From protein biomarkers to proteomics in dementia with Lewy Bodies. Ageing Res. Rev. 2023, 83, 101771.
96. Baba, T.; Kikuchi, A.; Hirayama, K.; Nishio, Y.; Hosokai, Y.; Kanno, S.; Hasegawa, T.; Sugeno, N.; Konno, M.; Suzuki, K.; et al. Severe olfactory dysfunction is a prodromal symptom of dementia associated with Parkinson’s disease: A 3 year longitudinal study. Brain 2012, 135, 161–169.
97. Domellof, M.E.; Lundin, K.F.; Edstrom, M.; Forsgren, L. Olfactory dysfunction and dementia in newly diagnosed patients with Parkinson’s disease. Park. Relat. Disord. 2017, 38, 41–47.
98. Fullard, M.E.; Morley, J.F.; Duda, J.E. Olfactory Dysfunction as an Early Biomarker in Parkinson’s Disease. Neurosci. Bull. 2017, 33, 515–525.
99. Chiasserini, D.; Biscetti, L.; Eusebi, P.; Salvadori, N.; Frattini, G.; Simoni, S.; De Roeck, N.; Tambasco, N.; Stoops, E.; Vanderstichele, H.; et al. Differential role of CSF fatty acid binding protein 3, alpha-synuclein, and Alzheimer’s disease core biomarkers in Lewy body disorders and Alzheimer’s dementia. Alzheimers Res. Ther. 2017, 9, 52.
100. Jellinger, K.A.; Korczyn, A.D. Are dementia with Lewy bodies and Parkinson’s disease dementia the same disease? BMC Med. 2018, 16, 34.
101. Sepe, F.N.; Chiasserini, D.; Parnetti, L. Role of FABP3 as biomarker in Alzheimer’s disease and synucleinopathies. Future Neurol. 2018, 13, 199–207.
102. Sezgin, M.; Bilgic, B.; Tinaz, S.; Emre, M. Parkinson’s Disease Dementia and Lewy Body Disease. Semin. Neurol. 2019, 39, 274–282.

103. Walker, L.; Stefanis, L.; Attems, J. Clinical and neuropathological differences between Parkinson’s disease, Parkinson’s disease dementia and dementia with Lewy bodies—Current issues and future directions. J. Neurochem. 2019, 150, 467–474.

104. Parnetti, L.; Gaetani, L.; Eusebi, P.; Paciotti, S.; Hansson, O.; El-Agnaf, O.; Mollenhauer, B.; Blennow, K.; Calabresi, P. CSF and blood biomarkers for Parkinson’s disease. Lancet Neurol. 2019, 18, 573–586.

105. Triozzi, P.L.; Stirling, E.R.; Song, Q.; Westwood, B.; Kooshki, M.; Forbes, M.E.; Holbrook, B.C.; Cook, K.L.; Alexander-Miller, M.A.; Miller, L.D.; et al. Circulating Immune Bioenergetic, Metabolic, and Genetic Signatures Predict Melanoma Patients’ Response to Anti-PD-1 Immune Checkpoint Blockade. Clin. Cancer Res. 2022, 28, 1192–1202.

106. Lu, Z.; Priya Rajan, S.A.; Song, Q.; Zhao, Y.; Wan, M.; Aleman, J.; Skardal, A.; Bishop, C.; Atala, A.; Lu, B. 3D scaffold-free microlivers with drug metabolic function generated by lineage-reprogrammed hepatocytes from human fibroblasts. Biomaterials 2021, 269, 120668.

107. Sinclair, E.; Trivedi, D.K.; Sarkar, D.; Walton-Doyle, C.; Milne, J.; Kunath, T.; Rijs, A.M.; de Bie, R.M.A.; Goodacre, R.; Silverdale, M.; et al. Metabolomics of sebum reveals lipid dysregulation in Parkinson’s disease. Nat. Commun. 2021, 12, 1592.

108. Oizumi, H.; Sugimura, Y.; Totsune, T.; Kawasaki, I.; Ohshiro, S.; Baba, T.; Kimpara, T.; Sakuma, H.; Hasegawa, T.; Kawahata, I.; et al. Plasma sphingolipid abnormalities in neurodegenerative diseases. PLoS ONE 2022, 17, e0279315.