FGF14 in Neurodegenerative Diseases: Research Advances (Postprint)

Authors: Wang Baohui, promise, Yang Dan, Li Xiaokun

Date: 2018-11-17T00:00:00+00:00

Abstract

Fibroblast growth factor 14 (FGF14) is a member of the fibroblast growth factor family, predominantly expressed in the developing and mature nervous system. Studies have found that FGF14 plays an important role in spinocerebellar ataxia type 27, a degenerative neurological disorder. The function of FGF14 is closely related to various ion channels, primarily sodium channels, and its activity is regulated by neuronal excitability. Based on the characteristics of FGF14, this article summarizes the current research progress on FGF14, providing a theoretical basis for basic and engineered studies of FGF14.

Full Text

Preamble

Research Progress of FGF14 in Neurodegenerative Diseases

WANG Baohui[1], XU Nuo[1], YANG Dan[1], LI Xiaokun[1,2]**
[1]College of Life and Environmental Sciences, Wenzhou University, Wenzhou 325035, Zhejiang, China
[2]Wenzhou Medical University, Wenzhou 325035, Zhejiang, China

Abstract

Fibroblast growth factor 14 (FGF14) is a member of the fibroblast growth factor family that is primarily expressed in the developing and mature nervous system. Research has revealed that FGF14 plays an important role in spinocerebellar ataxia type 27 (SCA27), a neurodegenerative disorder. The function of FGF14 is closely associated with various ion channels, particularly sodium channels, and its activity is regulated by neuronal excitability. Based on the characteristics of FGF14, this review summarizes current research progress and provides a theoretical foundation for basic and engineering studies of FGF14.

Keywords: FGF14; Spinocerebellar Ataxia (SCA); Hippocampal Neurons; Ion Channels

Fibroblast growth factor 14 (FGF14) belongs to the fibroblast growth factor family. Fibroblast growth factors (FGFs) are present in the central and peripheral nervous systems during development and throughout life, playing important roles in embryonic development, angiogenesis, and tissue repair [1]. The FGF family comprises 22 members divided into seven subfamilies: FGF1/2, FGF4/5/6, FGF3/7/10/22, FGF8/17/18, FGF9/16/20, FGF19/21/23, and FGF11/12/13/14. FGF14, together with FGF11, FGF12, and FGF13, belongs to the same subfamily known as the FGF homologous factor family (iFGF) [2][3], as shown in [Figure 1: see original paper]. This family exhibits high sequence tandem repeats and structural homology with fibroblast growth factors and has high affinity for heparin, but it cannot activate fibroblast growth factor receptors (FGFRs) or bind to FGFRs. Instead, it elicits cellular activity intracellularly [4] and is not secreted in detectable amounts from native or transfected cells [5]. FGF14 was first cloned in 2003 [6]. Human FGF14 is encoded by 252 amino acids with a molecular weight of 27 kDa and an isoelectric point of approximately 9.6.

The FGF14 gene is located at position 13q34 on chromosome 13 and consists of five exons [7]. FGF14 is localized to the axonal initial segment (AIS) [8-10] and has multiple isoforms (1a, 1b, 2, 3, 4, 5, 6, 7, 8, 9), primarily divided into FGF14-1a and FGF14-1b. These two isoforms differ mainly in their first exon: FGF14-1a is encoded by 247 amino acids, while FGF14-1b is encoded by 252 amino acids. FGF14-1a is primarily located in the nucleus, whereas FGF14-1b is mainly cytoplasmic [11]. FGF14-1a shares sequence homology with FGF12-1a and FGF13-1a, while the amino terminus of FGF14-1b contains a unique 69-amino-acid sequence and represents the more prevalent isoform in the central nervous system (CNS) [12].

Mouse FGF14 has two isoforms located on chromosome 14. The mouse FGF14a isoform shares 98.8% amino acid sequence identity with human FGF14-1a, differing by only three amino acids, while the mouse FGF14b isoform shares 99% identity with human FGF14-1b, differing by only two amino acids. Human tissues predominantly express FGF14-1b, which plays a more important role in disease pathogenesis.

Structurally, iFGF subfamily members display the same -trefoil core supporting 12 antiparallel -strands as FGFs, but iFGF family members lack a secretory signal peptide [13]. They share 58%-71% amino acid sequence identity with other growth factor members while retaining core amino acid residues in exons 2 and 3. iFGFs directly interact with the pore-forming -subunits of voltage-gated sodium channels (Nav) and modulate their gating properties and density [3,14,15].

FGF14 was initially discovered to be expressed in the developing brain, spinal cord, and thymus [11], but further research has confirmed that FGF14 is primar-

ily expressed in the developing and mature nervous system, with high expression in the CNS [16]. Clinical studies have identified an important association between FGF14 and spinocerebellar ataxia (SCA27). Additionally, research has demonstrated that FGF14 plays important roles in regulating the excitability of Purkinje neurons and modulating sodium, calcium, and potassium channels [17].

2 FGF14 and Neurodegenerative Diseases

Spinocerebellar ataxias (SCAs) constitute a heterogeneous group of degenerative disorders characterized by cerebellar and brainstem dysfunction and associated pathways, following an autosomal dominant inheritance pattern [18]. SCAs belong to the autosomal dominant cerebellar ataxias, which are heterogeneous neurological diseases featuring progressive cerebellar ataxia, often manifesting as paroxysmal dyskinesia and cognitive impairment [19-20].

SCAs can occur in infants, adolescents, and middle-aged adults. In adults, symptoms often begin with tremor [6,7,21], while infantile onset produces tremor within the first year of life. With age, patients gradually develop declining motor skills and ataxia symptoms with intellectual disability [21]. In adults, SCA27 presents with gait disturbance, dyskinesia, memory and executive dysfunction, low IQ, and nystagmus. Epidemiological studies show that in families with hereditary ataxia, affected members have significantly lower education levels [21], and the disease exhibits familial inheritance characteristics.

To date, more than 30 types of spinocerebellar ataxia have been identified. Clinical investigations have revealed that FGF14 is closely associated with spinocerebellar ataxia type 27 (SCA27), a rare cause of familial ataxia and an autosomal dominant disorder. SCA27 is a natural neurodegenerative disease, and its pathogenesis is currently thought to involve a novel role for FGF14 in synaptic plasticity [22]. Studies have found that the F145S mutation in exon 4 of FGF14 causes SCA27 [21,23,24], while FGF14 haploinsufficiency [25] and frameshift mutations [7,26] also cause SCA27. Additionally, exon deletion in FGF14 can trigger episodic ataxias (EAs) [23]. Mouse studies have shown that FGF14 knockout (FGF14-/-) mice can survive and reproduce but develop paroxysmal dyskinesia and spatial learning deficits, symptoms identical to human ataxia [9,21,23]. Beyond human and mouse studies, current research in lambs has demonstrated that FGF14 is associated with spinocerebellar ataxia in sheep, with mutated lambs displaying spontaneous and positional nystagmus and clinical dysfunction. Therefore, experiments in humans, mice, and lambs collectively demonstrate that abnormalities in the FGF14 gene cause spinocerebellar ataxia.

Alzheimer' s disease (AD) is a neurodegenerative disease prevalent in the elderly, characterized by progressive loss of memory and other cognitive functions. Studies in AD have found that functional enrichment of single nucleotide polymorphisms (SNPs) in AD patients shows that FGF14 is significantly overexpressed in AD due to its phosphorylation by JNK, and FGF14 mRNA is overexpressed

in patients with early-onset Alzheimer's disease [27]. Currently, applying FGF14 as an exogenous protein to PC12 cells in AD models has shown that FGF14 possesses good neuroprotective effects. Based on this existing interaction between FGF14 and AD, it is hypothesized that FGF14 is associated with Alzheimer' s disease.

3.1 Role of FGF14 in Regulating Hippocampal Neuronal Synaptic Plasticity

FGF14 is expressed in hippocampal pyramidal neurons and the dentate gyrus [14,28], and studies have demonstrated that FGF14 protein functions in hippocampal function. Short-term and long-term potentiation (LTP) studies in the hippocampus of FGF14 knockout mice have shown that synaptic plasticity is impaired in FGF14-/- mice, and FGF14 deficiency causes a reduction in synaptic vesicle number, indicating that FGF14 loss is directly associated with impaired synaptic plasticity. FGF14 contributes to short-term and long-term synaptic plasticity by regulating vesicle release probability and presynaptic mechanisms, establishing FGF14 as a regulator of synaptic plasticity [11,29]. FGF14 is essential for normal hippocampal synaptic function, and its loss affects synaptic activity in the dentate gyrus, impairing neuronal synaptic integration in the dentate gyrus circuit [10]. In summary, these findings demonstrate that FGF14 plays a significant role in regulating hippocampal neuronal synaptic plasticity.

3.2 FGF14 Regulates Cellular Excitability

Research has shown that FGF14 is associated with Nav channels. In Purkinje neurons lacking FGF14, Nav1.6 expression is reduced, leading to impaired cellular firing [13,30]. The fundamental regulatory feature of FGF14 in cerebellar Purkinje neurons is to slow Nav channel inactivation to promote resurgent currents [31]. FGF14 modulates excitability in the hippocampus and granule cell layer [3,28,29,32], and FGF14 deficiency is accompanied by changes in excitability of cerebellar granule and Purkinje neurons [33,34]. Disruption of FGF14 reduces FGF14 expression at the AIS, decreasing Nav channel density and hippocampal neuronal excitability [35].

3.3 FGF14 and Ion Channels

FGF14 interacts with the C-terminus of the -subunit of Nav channels, regulating the cell surface expression of Nav channel -subunits [8,35]. FGF14 effectively modulates the amplitude and voltage-dependence of Na+ currents in a channel isoform- and cell context-dependent manner, producing functional consequences in Na+ current amplitude and direction [3,8,14].

FGF14 has an inseparable relationship with Na+ channels, with two main isoforms, FGF14-1a and FGF14-1b, differentially regulating currents generated by Nav1.2 and Nav1.6 channels. The functional modulation by iFGF and Nav chan-

nels can be isoform-specific. For example, co-expression of Nav channels with FGF14-1b significantly reduces Nav1.5 and Nav1.1 current density and modulates the voltage-dependence of inactivation of both channels in opposite directions, whereas FGF14-1a inhibits Nav1.5 but not Nav1.1, and no longer inhibits Nav1.5 with current and depolarized Nav1.1 activation [14]. Co-expression of Nav channels with FGF14-1a (but not FGF14-1b) alters the voltage-dependence of Nav1.2 current inactivation, while FGF14-1b (but not FGF14-1a) changes the voltage-dependence of Nav1.2 current activation [8]. Although the protein domains of FGF14-1a and FGF14-1b share limited conserved sequences, both FGF14-1a and FGF14-1b target the AIS [14]. Studies in Purkinje neurons have found that compared to disruption of Nav1.6 function in normal granule cell layers, disruption of Nav1.6 function in FGF14-/- Purkinje neurons has a greater impact on motor control and coordination, with reduced Nav1.6 expression in FGF14-/- Purkinje neurons [14,34]. In Purkinje neurons expressing FGF14b, the main regulatory component of Nav current resides within the N-terminus of FGF14b [31]. However, when expressed in hippocampal neurons, the FGF14b F150S mutant reduces Nav channel current and inhibits neuronal excitability in a dominant-negative manner [36]. Current research indicates that glycogen synthase kinase 3 (GSK3) provides a novel target for the FGF14-Nav complex. FGF14 controls Nav channels located at the AIS, and through a GSK-3-centered network, can regulate AIS localization and modulate neuronal excitability [33]. Pharmacological inhibition of GSK3 reduces the assembly of FGF14 and Nav1.2 channels, alters the functional modulation of Nav1.6 by FGF14, modifies FGF14-dependent Na+ current modulation, and induces subcellular redistribution of native FGF14-Nav channel complexes in hippocampal neurons [9]. Studies of casein kinase 2 (CK2) have revealed that CK2 is required for FGF14-Nav interaction and neuronal excitability. CK2 is a priming kinase for GSK-3, and when the potent CK2 inhibitor TBB (4,5,6,7-tetrabromobenzotriazole) is applied, it rapidly eliminates FGF14-Nav1.6 interaction and reduces the ability of FGF14 to bind Nav1.6 and Nav1.2.

FGF14 is a key auxiliary protein that interacts with ion channels. FGF14 deficiency downregulates Nav current activity [37], and FGF14 not only acts on Nav channels but also regulates Ca2+ channels. Studies have shown that endogenous FGF14 affects Ca2+ channels in granule cells, and FGF14 can modulate presynaptic Cav2.1 and Cav2.2 Ca2+ channels [36]. FGF14 is also crucial for regulating KCNQ2 channels in hippocampal neurons, as FGF14-/- leads to loss of KCNQ2 at the AIS and reduces KCNQ2/3 currents.

As a member of the fibroblast growth factor family, FGF14 has multiple biological functions within cells. FGF14 is known to play important roles in SCAs and holds rich potential value for research in neurodegenerative diseases. Our research has demonstrated that FGF14 possesses certain biological activity as an exogenous protein and exhibits neuroprotective effects when applied to A - induced PC12 cell models of AD. However, the specific mechanisms of FGF14 action in nervous system diseases and the detailed functions of FGF14 as an exogenous protein remain unclear, necessitating further in-depth investigation.

[1] Zhou Y, Wang Z, Li J, et al. Fibroblast growth factors in the management of spinal cord injury.[J]. Journal of cellular and molecular medicine, 2017, 22(1).
[2] Beenken A, Mohammadi M. The FGF family: biology, pathophysiology and therapy[J]. Nature Reviews Drug Discovery, 2009, 8(3):235-253.
[3] Laezza F, Gerber B R, Lou J Y, et al. The FGF14(F145S) mutation disrupts the interaction of FGF14 with voltage-gated Na+ channels and impairs neuronal excitability.[J]. Journal of Neuroscience the Official Journal of the Society for Neuroscience, 2007, 27(44):12033-44.
[4] Li X, Wang C, Xiao J, et al. Fibroblast growth factors, old kids on the new block[J]. Seminars in Cell & Developmental Biology, 2016, 53:155-167.
[5] Schoorlemmer J, Goldfarb M. Fibroblast growth factor homologous factors are intracellular signaling proteins.[J]. Current Biology, 2001, 11(10):793-797.
[6] Swieten J C V, Brusse E, Graaf B M D, et al. A Mutation in the Fibroblast Growth Factor 14, Gene Is Associated with Autosomal Dominant Cerebral Ataxia[J]. American Journal of Human Genetics, 2003, 72(1):191-199.
[7] Dalski A, Atici J, Kreuz F R, et al. Mutation analysis in the fibroblast growth factor 14 gene: frameshift mutation and polymorphisms in patients with inherited ataxias.[J]. European Journal of Human Genetics Ejhg, 2005, 13(1):118.
[8] Laezza F, Lampert A, Kozel M A, et al. FGF14 N-terminal splice variants differentially modulate Nav1.2 and Nav1.6-encoded sodium channels[J]. Molecular & Cellular Neurosciences, 2009, 42(2):90.
[9] Shavkunov A S, Wildburger N C, Nenov M N, et al. The fibroblast growth factor 14 • voltage-gated sodium channel complex is a new target of glycogen synthase kinase 3 (GSK3)[J]. Journal of Biological Chemistry, 2013, 288(27):19370-19385.
[10] Alshammari M A, Alshammari T K, Nenov M N, et al. Fibroblast Growth Factor 14 Modulates the Neurogenesis of Granule Neurons in the Adult Dentate Gyrus[J]. Molecular Neurobiology, 2016, 53(10):7254-7270.
[11] Wang Q, Mcewen D G, Ornitz D M. Subcellular and developmental expression of alternatively spliced forms of fibroblast growth factor 14.[J]. Mechanisms of Development, 2000, 90(2):283-287.
[12] Munozsanjuan I, Smallwood P M, Nathans J. Isoform diversity among fibroblast growth factor homologous factors is generated by alternative promoter usage and differential splicing.[J]. Journal of Biological Chemistry, 2000, 275(4):2589-97.
[13] Wang Q, Bardgett M E, Wong M, et al. Ataxia and Paroxysmal Dyskinesia in Mice Lacking Axonally Transported FGF14[J]. Neuron, 2002, 35(1):25-38.
[14] Lou J Y, Laezza F, Gerber B R, et al. Fibroblast growth factor 14 is an intracellular modulator of voltage-gated sodium channels.[J]. Journal of Physiology, 2005, 569(1):179–193.
[15] Rush A M, Wittmack E K, Tyrrell L, et al. Differential modulation of sodium channel Na(v)1.6 by two members of the fibroblast growth factor homologous factor 2 subfamily.[J]. European Journal of Neuroscience, 2006, 23(10):2551-2562.
[16] Alshammari T K, Alshammari M A, Nenov M N, et al. Genetic deletion

of fibroblast growth factor recapitulates phenotypic alterations underlying cognitive impairment associated with schizophrenia[J]. Translational Psychiatry, 2016, 6(5):e806.
[17] Pablo J L, Pitt G S. FGF14 is a regulator of KCNQ2/3 channels[J]. Proceedings of the National Academy of Sciences of the United States of America, 2017, 114(1):154.
[18] Shakkottai V G, Fogel B L. Clinical Neurogenetics : Autosomal Dominant Spinocerebellar Ataxia[J]. Neurologic Clinics, 2013, 31(4):987-1007.
[19] Peter Bauer, Thorsten Schulte, Ludger Schöls. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis[J]. Lancet Neurology, 2004, 3(5):291-304.
[20] Taroni F, Didonato S. Pathways to motor incoordination: the inherited ataxias.[J]. Nature Reiview Neuroscience, 2004, 5(8):641.
[21] Brusse E, De Koning I, Maat-Kievit A, et al. Spinocerebellar ataxia associated with a mutation in the fibroblast growth factor 14 gene (SCA27): A new phenotype.[J]. Movement Disorders, 2006, 21(3):396–401.
[22] Teive H A G, Arruda W O. Cognitive dysfunction in spinocerebellar ataxias[J]. Dementia & Neuropsychologia, 2009, 3(3):180-187.
[23] Choquet K, La P R, Brais B. A novel frameshift mutation in FGF14 causes an autosomal dominant episodic ataxia.[J]. Neurogenetics, 2015, 16(3):233-236.
[24] Coebergh J A, De F V D P, Snoeck I N, et al. A new variable phenotype in spinocerebellar ataxia 27 (SCA 27) caused by a deletion in the FGF14 gene[J]. European Journal of Paediatric Neurology, 2014, 18(3):413-415.
[25] Misceo D, Fannemel M, Barøy T, et al. SCA27 caused by a chromosome translocation: further delineation of the phenotype[J]. Neurogenetics, 2009, 10(4):371-374.
[26] Soong B W, Paulson H L. Spinocerebellar ataxias: an update.[J]. Current Opinion in Neurology, 2007, 20(4):438-446.
[27] Re J D, Wadsworth P A, Laezza F. Intracellular Fibroblast Growth Factor 14: Emerging Risk Factor for Brain Disorders[J]. Frontiers in Cellular Neuroscience, 2017, 11.
[28] Xiao M, Xu L, Laezza F, et al. Impaired hippocampal synaptic transmission and plasticity in mice lacking fibroblast growth factor 14[J]. Molecular & Cellular Neuroscience, 2007, 34(3):366-377.
[29] Wozniak D F, Xiao M, Xu L, et al. Impaired spatial learning and defective theta burst induced LTP in mice lacking fibroblast growth factor 14[J]. Neurobiology of Disease, 2007, 26(1):14.
[30] Cody J D, Heard P, Hale D. Identification of two novel chromosome regions associated with isolated growth hormone deficiency.[J]. Journal of Pediatric Endocrinology & Metabolism Jpem, 2010, 23(11):1159-64.
[31] Yan H, Pablo J L, Wang C, et al. FGF14 modulates resurgent sodium current in mouse cerebellar Purkinje neurons[J]. Elife, 2014, 3(3):e04193.
[32] Goldfarb M, Schoorlemmer J, Williams A, et al. Fibroblast Growth Factor Homologous Factors Control Neuronal Excitability through Modulation of Voltage-Gated Sodium Channels[J]. Neuron, 2007, 55(3):449-463.
[33] Bosch M K, Nerbonne J M, Townsend R R, et al. Proteomic analysis of

native cerebellar iFGF14 complexes[J]. Channels, 2016, 10(4):297-312.
[35] Hsu W J, Scala F, Nenov M N, et al. CK2 activity is required for the interaction of FGF14 with voltage-gated sodium channels and neuronal excitability.[J]. Faseb Journal Official Publication of the Federation of American Societies for Experimental Biology, 2016, 30(6):2171.
[34] Shakkottai V G, Xiao M, Xu L, et al. FGF14 regulates the intrinsic excitability of cerebellar Purkinje neurons. Neurobiol Dis[J]. Neurobiology of Disease, 2009, 33(1):81.
[36] Yan H, Pablo J, Pitt G. FGF14 Regulates Presynaptic Ca 2+, Channels and Synaptic Transmission[J]. Cell Reports, 2013, 4(1):66.
[37] Wildburger N C, Laezza F. Control of neuronal ion channel function by glycogen synthase kinase-3: new prospective for an old kinase[J]. Frontiers in Molecular Neuroscience, 2012, 5:80.

Note: Figure translations are in progress. See original paper for figures.