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REVIEW

Bernhard Reuss · Oliver von Bohlen und Halbach

Fibroblast growth factors and their receptors in the central nervous system

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Abstract Fibroblast growth factors (FGFs) and their receptors constitute an elaborate signaling system that participates in many developmental and repair processes of virtually all mammalian tissues. Among the 23 FGF members, ten have been identified in the brain. Four FGF receptors (FGFRs), receptor tyrosine kinases, are known so far. Ligand binding of these receptors greatly depends on the presence of heparan sulfate proteoglycans, which act as low affinity FGFRs. Ligand binding specificity of FGFRs depends on the third extracellular Ig-like domain, which is subject to alternative splicing. Activation of FGFRs triggers several intracellular signaling cascades. These include phosphorylation of src and PLCγ leading finally to activation of PKC, as well as activation of Crk and Shc. SNT/FRS2 serves as an alternative link of FGFRs to the activation of PKC and, in addition, activates the Ras signaling cascade. In the CNS, FGFs are widely expressed; FGF-2 is predominantly synthesized by astrocytes, whereas other FGF family members, e.g., FGF-5, FGF-8, and FGF-9, are primarily synthesized by neurons. During CNS development FGFs play important roles in neurogenesis, axon growth, and differentiation. In addition, FGFs are major determinants of neuronal survival both during development and during adulthood. Adult neurogenesis depends greatly on FGF-2. Finally, FGF-1 and FGF-2 seem to be involved in the regulation of synaptic plasticity and processes attributed to learning and memory.

Keywords Fibroblast growth factors · Central nervous system · Signaling system · Receptor tyrosine kinases · Heparan sulfate proteoglycans · Ligand binding specificity

B. Reuss (✉) · O. von Bohlen und Halbach
Department of Neuroanatomy
and Interdisciplinary Center for Neurosciences (IZN),
University of Heidelberg,
Im Neuenheimer Feld 307, 69120 Heidelberg, Germany
e-mail: bernhard.reuss@urz.uni-heidelberg.de
Tel.: +49-6221-548228
Fax: +49-6221-545604

Introduction

Development and functions of the mammalian central nervous system (CNS) as well as its adaptation to changing demands require numerical and functional plasticity of all cell types, most notably neurons and their synaptic terminals. Such changes depend to a large extent on cytokine signaling networks, whose complexities are still largely enigmatic. Members of the fibroblast growth factor (FGF) family expressed in the nervous system serve as important signals during developmental and repair processes.

Starting with the isolation and cloning of the first FGF family member in the mid-eighties of the last century (FGF-2; Abraham et al. 1986a, 1986b), the FGF family has increased in number and complexity; 23 family members and four receptors are known to date (Powers et al. 2000), whose gene and protein structures and intracellular signaling cascades have been extensively explored (Ornitz and Itoh 2001; Powers et al. 2000). Not all FGF subtypes can be detected in all species, including humans and mice. For example, FGF-15 has not been identified in the human genome, and FGF-19 could not be detected in mice, resulting in a total of only 22 FGF family members in each of these species. FGF and FGF receptor (FGFR) knockout animals have significantly advanced our knowledge of the biological significance of ligand and receptor molecules (Ornitz and Itoh 2001). With regard to functions of FGFs in the CNS, these and other studies have demonstrated important roles of FGFs in neurogenesis, differentiation, axonal branching, and neuron survival. FGFs are important in repair processes following different types of brain and peripheral nerve lesions and degenerative disorders (Haynes 1988; Mocchetti and Wrathall 1995). Last but not least, in the adult brain FGFs are involved in cognitive processes including learning and memory (Calamandrei and Alleva 1995).

Basic aspects of fibroblast growth factor signaling

Gene structure and evolutionary history of fibroblast growth factors

All known FGF genes consist of three coding exons, with exon 1 containing the start codon. However, some FGF genes, e.g., FGF-2 and FGF-3, contain additional 5' untranscribed regions initiating from upstream CUG codons (Kiefer et al. 1994; Arnaud et al. 1999). The size of the coding region of FGF genes ranges from under 5 kb (FGF-3 and FGF-4) to over 100 kb (FGF-12). In certain FGF subfamilies, exon 1 is subdivided into two or four alternatively spliced subexons (1A–1D for FGF-8), with a single initiation codon residing in exon 1A. Other family members (e.g., FGF-11 to -14) have alternatively spliced amino-terminal regions resulting from the use of alternative 5' exons.

With respect to their chromosomal localization, FGF genes show a widely scattered distribution. With the exception of FGF-16, the chromosomal localization for all human FGF genes is known. Several human FGF genes are clustered on distinct chromosomal regions. For example, genes encoding FGF-3, FGF-4 and FGF-19 are located on chromosome 11q13, being separated by only 40 and 10 kb, respectively. Furthermore, the FGF-6 and FGF-23 genes are located in a small 55-kb fragment of chromosome 12p13. The FGF-17 gene and FGF-20 gene also reside together on chromosome 8p21–8p22 (Kelley et al. 1992). For the mouse, localization of 16 FGF genes has been determined, revealing some similarities to their arrangement on human chromosomes. For example, the genes encoding FGF-3, FGF-4 and FGF-19 are linked on an 80-kb stretch of chromosome 7F, and FGF-6 and FGF-23 on chromosome 6F3-G1 (Ornitz and Itoh 2001).

Concerning their evolutionary development, FGFs are comparably old molecules that evolved in invertebrates. FGF-like genes have also been identified in several viral genomes (Li et al. 2002). However, genomes of unicellular organisms, such as *E. coli* or yeast (*S. cerevisiae*), contain no FGF-like genes. With regard to *Drosophila* and *Caenorhabditis elegans,* the most important invertebrate model organisms, only one FGF-like sequence (branchless) has been revealed for *Drosophila* (Sutherland et al. 1996) and two (egl-17 and let-756) for *C. elegans* (Burdine et al. 1997; Coulier et al. 1997). Across species, FGF proteins are highly conserved and share greater than 90% amino-acid sequence homology. To date, four FGFs have been identified in zebrafish (FGF-3, -8, -17, and -18), six in the clawed toad *Xenopus* (FGF-3, Fgfi, Fgfii, FGF-8, -9, and -20), and seven in chicken (FGF-2, -4, -8, -12, -14, -18, and -19).

Human FGFs show different degrees of sequence and functional homologies, and thereby may be grouped in several subfamilies. One such subfamily comprises FGF-8, -17 and -18, which share 70–80% of their amino acid sequences, revealing high degrees of similarity in receptor binding specificity and showing partially overlapping expression sites, e.g., the midbrain-hindbrain boundary.

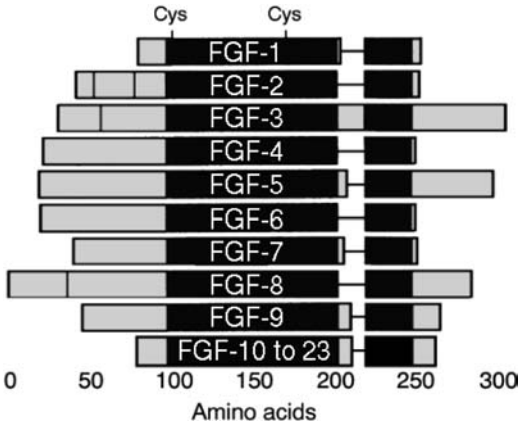

Fig. 1 Schematic domain alignment of different members of the FGF family of protein growth factors. All FGFs consist of two highly conserved core-domains (*black*), separated by a central spacer region of variable length. Also C- and N-terminal regions differ in their length, with some FGFs (FGF-2, FGF-3 and FGF-9 bearing alternative splice sites for their N-terminal regions) (modified from Bieger and Unsicker 1996)

However, the chromosomal locations of these factors over the whole genome suggest that gene translocation and genome duplication rather than local duplication events may have led to their formation.

FGF protein structure

Vertebrate FGF proteins range in molecular weight from 17 to 34 kDa, whereas the translation product of the *Drosophila* FGF homolog *branchless* is 84 kDa. General protein structure is similar in all FGFs, with an internal core region consisting of 28 highly conserved and six identical amino-acid residues (Fig. 1; Ornitz 2000). Ten of these conserved residues are responsible for interactions with the FGF receptor (Plotnikov et al. 2000). In FGF-1 and FGF-2 the core domain of the protein consists of 12 antiparallel β-strands (Fig. 2; Zhu et al. 1991; Eriksson et al. 1991). Two of these β-strands (Fig. 2: β10 and β11) contain basic amino acid residues forming the heparin-binding site on FGF-2 (Moy et al. 1996; Li et al. 1994).

Subcellular localization and secretion of FGFs

The majority of FGFs (FGFs-3 to -8, -10, -15, -17 to -19, and -21 to -23) possess amino-terminal signal peptides and, therefore, may be assumed to be readily secreted from cells. However, FGF-1, -2, -9, -16 and -20 lack conventional signal peptides but, nevertheless, are secreted into the extracellular space (Miyake et al. 1998; Miyamoto et al. 1993; Ohmachi et al. 2000). FGF-1 and -2 are probably released upon cell damage and may be released from damaged cells by a mechanism that is independent of the endoplasmic reticulum-Golgi pathway

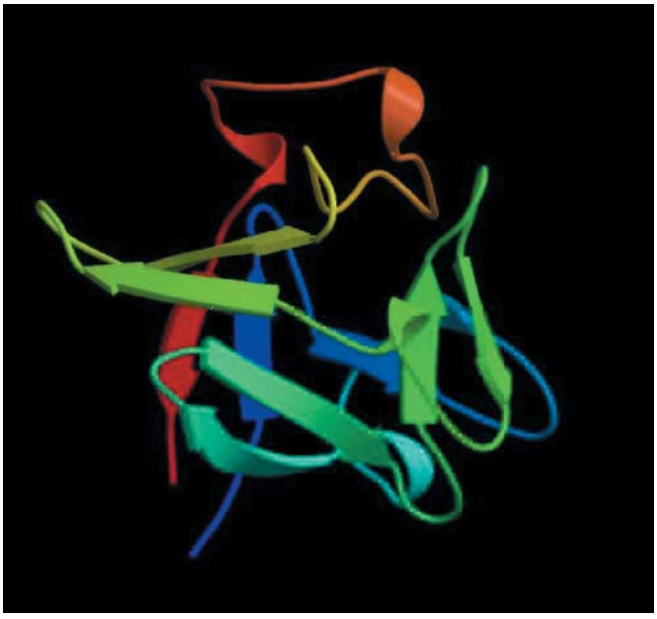

Fig. 2 Three-dimensional structure of the FGF-2 protein (modified from Zhu et al. 1991)

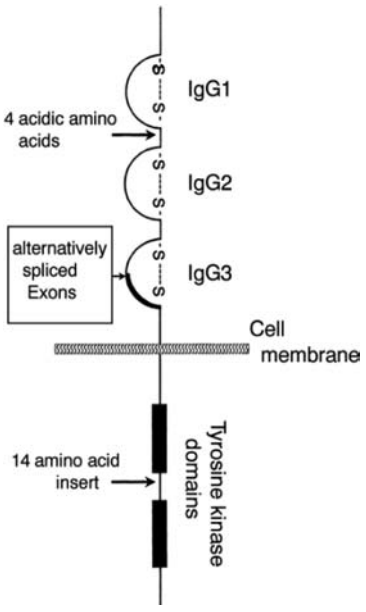

Fig. 3 Structure of the fibroblast growth factor receptors. Receptors consist of three extracellular Ig-like domains, a transmembrane domain and two intracellular tyrosine kinase domains. An acidic domain of four amino acids is important for heparin binding and thus for receptor dimerization (modified from Bieger and Unsicker 1996)

(Mignatti et al. 1992; Friesel and Maciag 1999). FGF-9 possesses a non-cleaved amino-terminal hydrophobic sequence responsible for secretion (Miyakawa et al. 1999; Revest et al. 2000). For FGF-2 and FGF-3 high molecular weight forms with predominant nuclear localization have been demonstrated (Arnaud et al. 1999; Coulier et al. 1997; Antoine et al. 1997).

The fibroblast growth factor receptors

FGFs elicit a wide variety of effects in their target cells via activation of a group of cell-surface bound tyrosine kinase receptors. Existence of these so-called high affinity FGF receptors was first demonstrated in 3T3 fibroblasts, where FGF-1 and FGF-2 stimulated tyrosine phosphorylation as detected by phosophotyrosine-specific antibodies (Coughlin et al. 1988). Direct evidence for the existence of membrane-bound high affinity FGF receptors (K_D=20 pmol/l) came from binding studies with ^{125}I-labeled FGF-2 on BHK cells (Moscatelli 1987). Several cross-linking studies identified the receptor proteins responsible for this binding to be between 125 and 160 kDa in molecular weight (Neufeld and Gospodarowicz 1985, 1986; Friesel et al. 1986; Moenner et al. 1986; Blanquet et al. 1989).

A further breakthrough with regard to the characterization of FGF receptors was achieved by the isolation of a cDNA for a protein with high affinity for FGF-1 from chicken tissue (Lee et al. 1989). Structural characterization of this molecule led to the identification of the prototypic structural hallmarks of all FGF receptors, which are transmembrane proteins with three extracellular Ig-like domains (IgI, IgII, and IgIII), an acidic domain between IgI and IgII, a hydrophobic transmembrane domain, and an intracellular tyrosine kinase domain, respectively (Fig. 3; Johnson et al. 1990). Cloning of FGF receptor-1 and -2 (Dionne et al. 1990) identified them as being identical to the previously isolated tyrosine kinase proteins flg and bek, respectively (Kornbluth et al. 1988; Ruta et al. 1989). So far, four different subtypes of FGF receptors have been identified (Johnson and Williams 1993). Affinity of FGF receptors for their ligands is highly diverse with different affinities for each member of the FGF family of growth factors (Table 1).

Table 1 Receptor binding of FGF family members to the four FGF receptor subtypes (modified from Ornitz et al. 1996) (+ receptor binding, – no receptor binding, ? not investigated)

	FGFR-1	FGFR-2	FGFR-3	FGFR-4
FGF-1	+	+	+	+
FGF-2	+	+	+	+
FGF-3	+	+	–	–
FGF-4	+	+	+	+
FGF-5	+	+	–	–
FGF-6	+	+	–	+
FGF-7	–	+	–	–
FGF-8	+	+	+	+
FGF-9	–	+	+	+
FGF-10	–	+	–	–
FGF-11 to -16	?	?	?	?
FGF-17	–	+	+	+
FGF-18	–	–	+	+
FGF-19 to -23	?	?	?	?

The diversity of effects that different FGF family members exert upon different cell types of the CNS

Table 2 Activation of different FGF receptor splice variants by different FGF family members (modified from Ornitz et al. 1996). Each value represents the percentage of activation caused by FGF-1 with a given splice variant

FGFR	FGF-1	FGF-2	FGF-3	FGF-4	FGF-5	FGF-6	FGF-7	FGF-8	FGF-9
1, IIIb	100	60	34	16	4	5	6	4	4
1, IIIc	100	104	0	102	59	55	0	1	21
2, IIIb	100	9	45	15	5	5	81	4	7
2, IIIc	100	64	4	94	25	61	2.5	16	89
3, IIIb	100	1	2	1	1	1	1	1	42
3, IIIc	100	107	1	69	12	9	1	41	96
4	100	113	6	108	7	79	2	76	75

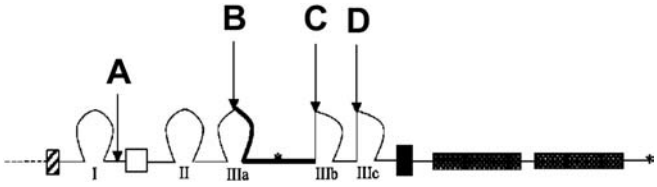

Fig. 4 Structure of the FGF-receptor gene. Four possible splice sites exist, leading either to molecules with a truncated C-terminal region or to molecules with different variants of the third Ig-like domain (IgIIIa, IgIIIb, and IgIIIc) (modified from Johnson et al. 1991)

depends, in part, on a significant structural and functional diversity of FGF receptors (Fig. 4). Diversity of FGF receptors beyond the four receptor subtypes is achieved by the generation of alternative splice variants of a given FGF receptor gene (Ornitz et al. 1996). The protein region with the highest impact on FGF receptor binding specificity is a portion of the IgIII domain for which three different splice variants termed IgIIIa, IgIIIb, and IgIIIc have been identified so far (for relative binding affinities of different FGF family members to the different IgIII splice variants see Table 2). While for FGFR1 and FGFR2 all three splice variants could be detected (Johnson et al. 1991; Chellaiah et al. 1994), FGFR3 occurs only as the IGIIIb and IGIIIc variants, and FGFR4 exclusively as the IgIIIc variant (Vainikka et al. 1992).

The FGF/FGFR complex and FGF-dependent intracellular signaling

Ligand binding to FGF receptors leads to the formation of a receptor complex consisting of two FGF molecules bound to a receptor, which are linked by a heparan sulfate proteoglycan molecule, e.g., heparin (Fig. 5). The consensus mechanism is thought to consist of the formation of two independent FGF/FGFR complexes which are subsequently connected by a heparin-like glycosaminoglycan (Venkatamaran et al. 1999; Stauber et al. 2000). Formation of the receptor complex triggers receptor activation by phosphorylation, leading to recruitment and phosphorylation of intracellular signaling molecules. An important class of signaling proteins known to bind to the activated FGF receptor complex belongs to the group of so-called src-homology2 (SH2) domain proteins. The common structural feature of these proteins is the SH2 domain that serves the intracellular

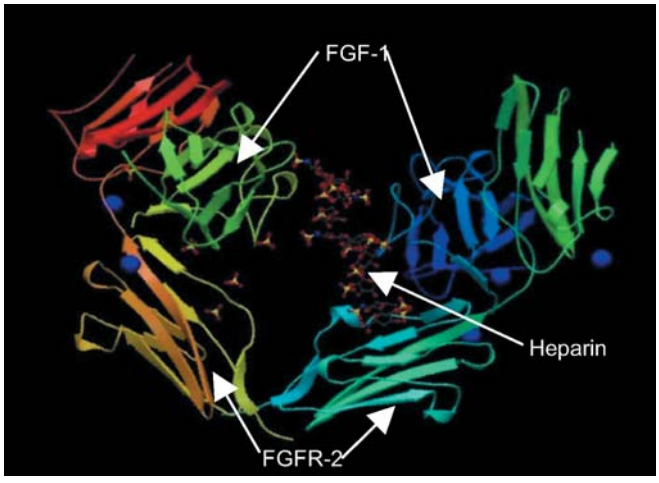

Fig. 5 Three-dimensional structure of the extracellular portion of a complex consisting of two FGF-1/FGFR-2 heterodimers, linked together by heparin (modified from Pellegrini et al. 2000)

interaction with the receptor complex. The SH2-containing proteins may serve as substrates for receptor-mediated phosphorylation themselves, or may function as adaptor proteins to recruit other target proteins. Tyrosine kinase receptors generally propagate signal transduction by phosphotyrosine-induced conformational changes in their target proteins resulting in activation of various catalytic activities.

Most studies on FGF receptor-mediated signal transduction have been carried out using FGFR-1 as the prototypical FGFR. The signaling pathways from different FGFRs are probably quite similar, owing to a high degree of homology at the amino acid level between different types of receptor (Johnson and Williams 1993). In addition, Raffioni et al. (1999) have shown, by using chimeric receptors composed of the cytoplasmic domains of FGFR-1, FGFR-3 and FGFR-4 linked to the extracellular domain of the PDGF receptor, that the principal difference between FGFRs is the strength of tyrosine kinase activity, and not any other differences in target proteins (Raffioni et al. 1999). This means that all FGFR subtypes drive the same signaling cascades, but with different strength.

Structure of the FGFR intracellular domain

There are seven tyrosine residues in the cytoplasmic tail of FGFR-1 that can be substrates for phosphorylation: Tyr463, Tyr583, Tyr585, Tyr653, Tyr654, Tyr730 and Tyr766. Tyr653 and Tyr654 are important for the catalytic activity of the activated FGFR and are essential for signaling (Mohammadi et al. 1996). Tyr766 has been shown to bind the SH2 domain of phospholipase Cγ (PLCγ) and is necessary for FGFR activation of PLCγ (Mohammadi et al. 1991). In contrast, the other tyrosines can be mutated to phenylalanine residues, which are not substrates for auto-phosphorylation, without loss of mitogen activated protein (MAP) kinase activity and mitogenic signaling in rat L-6 fibroblasts (Mohammadi et al. 1996). Their significance in FGFR signal transduction is therefore unknown. It is interesting to note that a 90-kDa phosphoprotein has been found to be associated with the adaptor molecule Grb2 following activation of both the wild-type and phenylalanine-mutated receptors. This suggests that FGFR signaling may not exclusively rely on the phosphotyrosine-SH2 pathway.

The PLCγ signaling pathway

PLCγ is a cytoplasmatic membrane-associated protein that cleaves phosphatidyl-inositol-4, 5-bisphosphate to inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 released by this process stimulates the release of calcium from the endoplasmic reticulum, while DAG and calcium activate protein kinase C (PKC). PLCγ was identified as a 150-kDa phosphoprotein associated with FGFR following ligand-dependent activation (Burgess et al. 1990), and this association is due to binding between the SH2 domain of PLCγ and Tyr766 of the receptor (Mohammadi et al. 1991). Two groups independently mutated this tyrosine to phenylalanine, showing that this residue is essential for phosphatidylinositol hydrolysis (Mohammadi et al. 1992; Peters et al. 1992). However, mutation of Tyr766 did not affect FGFR-mediated mitogenesis, neuronal differentiation (Spivak-Kroizman et al. 1994b), or mesoderm induction in a *Xenopus* animal cap model (Muslin et al. 1994). This implies either that PLCγ signaling is redundant with respect to mitogenesis and differentiation, or that the PLCγ pathway is important for some other functions of FGFR signaling. Although the PLCγ pathway is not directly involved in cell motility (Langgren et al. 1998), it may be involved in some other form of cytoskeletal alteration, as the actin-binding protein profilin participates in PLCγ signaling (Godschmidt-Clèrmont et al. 1991).

The src signaling pathway

Src is a non-receptor tyrosine kinase that may link FGFR signaling to cortactin (Zhan et al. 1993), a focal adhesion-associated protein that binds filamentous actin (Wu et al. 1991b). This connection would provide an alternate pathway to that of PLCγ for FGFR-mediated cytoskeletal alterations. However, there are conflicting reports concerning the interaction of FGFR and Src. Zhan et al. (1994) found a direct interaction by immunoprecipitation with recombinant FGFR-1. In contrast, Langren et al. (1995) saw no direct interaction and, instead, proposed that, as the Tyr766 to Phe766 mutant had high levels of phosphorylated Src, the PLCγ pathway inhibits Src activity.

Crk mediated signaling

Crk is a SH2/SH3 containing adaptor protein, which probably links FGFR to the downstream signaling molecules Shc, C3G and Cas, which may in turn propagate a mitogenic signal from FGFR. Larsson et al. (1999) have shown that Crk binds via its SH2 domain to Tyr463 of the activated FGFR. Signaling through Crk has no effect on cell motility, yet endothelial cells expressing FGFR-1 with a phenylalanine substitution at Tyr463 failed to proliferate, and the activity of both Erk2 and Jun kinases was suppressed. These results are in contradiction to those of Mohammadi et al. (1996), who determined that Tyr463 was not important for mitogenesis. Possibly, this discrepancy may reflect differences in FGFR signaling intrinsic to different cell types, as Mohammadi and coworkers used fibroblasts, while Larsson and associates worked with endothelial cells.

The SNT-1/FRS2 signaling pathway

By studying tyrosine-mutated FGFRs, an alternative tyrosine-phosphorylation-independent signaling pathway of FGF receptors has been shown to exist, involving a novel 90-kDa phosphoprotein that has been recently identified as SNT-1 (Wang et al. 1996) or FRS2 (Kouhara et al. 1997). Both groups demonstrated independently that SNT-1/FRS2 links the FGFR signaling to the Ras/MAPK signaling pathway, which is important for growth-factor-induced cell-cycle progression. Activation of SNT-1/FRS2 recruits the adaptor protein Grb-2/Sos that, in turn, recruits Ras to the FGFR complex (Kouhara et al. 1997). In addition to associating with Grb-2, activated FRS2 also binds the protein tyrosine phosphatase Shp2 (Ong et al. 2000). Ong et al. (1997) have shown by co-immunoprecipitation that Shp2 associates with both FRS2 and the docker protein Gab-1. SNT-1/FRS2 is localized to the inner leaflet of the cell membrane by myristylation and interacts with FGFR-1 at amino acids 407–433 of the juxtamembrane region (Xu et al. 1998). In addition to linking FGFR signaling to the Ras/MAPK pathway, Lim et al. (1999) have recently shown that SNT-1/FRS2 can link FGFR activation to atypical protein kinase C isotypes, although the precise role of this linkage with respect to mitogenesis or chemotaxis has yet to be characterized.

An important crosslink between FGFR1 dependent activation of SNT-1/FRS2 and signaling of neurotrophins is suggested by Ong et al. (2000) and by Yan et al. (2002). As shown by Ong et al. (2000), SNT-1/FRS2 is constitutively associated with FGFR1, independent of receptor activation. In addition, Yan et al. (2002) demonstrated that Trk neurotrophin receptors also utilize SNT-1/FRS2 in their signaling pathways, but in this case association of FRS2 with Trk receptors depends on receptor activation. As a consequence FGFR1 may regulate Trk signaling by sequestering FRS2 from ligand-bound Trk receptors.

In summary, FGFRs mediate signal transduction by at least two independent pathways. First, FGFRs utilize the canonical SH2-linked pathway joining FGFR directly to PLCγ and Crk, and probably indirectly to Src. Secondly, FGFR is linked to SNT1/FRS2 through an interaction at the juxtamembrane domain. Although this second pathway appears at least superficially analogous to that of the insulin receptor and the insulin receptor substrate (IRS)-1, its exact role has yet to be determined, as it seems to function independently of receptor phosphorylation (Yenush and White 1997).

FGF-knockout mice and transgenic mouse models

For most members of the FGF family, mutant mice with disruptions of the respective genes by homologous recombination have been generated. Phenotypes resulting from such knockouts range from early embryonic lethality to nearly undetectable changes in the adult. The comparably mild phenotypes in several FGF knockout mice might be explained by functional redundancy of different members of the FGF family, which may compensate for the loss of a single family member. This has been demonstrated for FGF-8 and -17, which are able to substitute one another during formation of the midbrain-hindbrain boundary (Xu et al. 2000). Phenotypes of the FGF knockout mice available so far are summarized in Table 3.

FGF functions in the central nervous system

A previous review from our laboratory (Bieger and Unsicker 1996) summarized work on FGFs in the CNS up to the mid-1990s. In the past 6 years significant progress has been made with regard to both fundamental and clinical aspects of FGF functions, most notably in the areas of developmental patterning, neurogenesis, axonal growth, neuroprotection, lesion repair, and learning and memory. As summarized in this review, most of the work has been done on neural functions of FGF-1 and FGF-2 (cf. Fig. 6), implying that understanding the roles of the other members of the FGF family expressed in the brain is still relatively fragmentary.

As demonstrated by a wide variety of studies, FGFs exert diverse effects on development (Vaccarino et al. 2001; Molteni et al. 2001) and maintenance of neurons

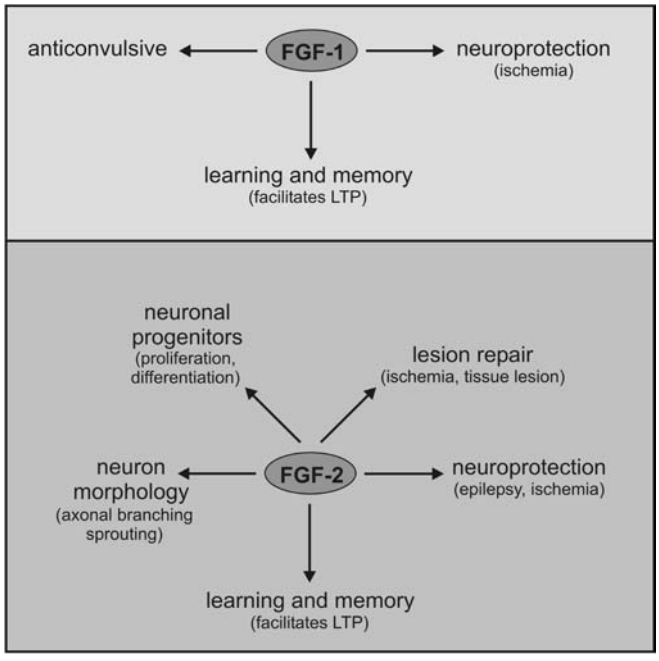

Fig. 6 In the central nervous system various positive effects of FGFs on neuronal structures have been demonstrated. In this figure, a schematic overview of the effects of FGF-1 and FGF-2 on hippocampal neurons is given

(Perrone-Capano and Di Porzio 2000; Mufson et al. 1999) including effects on fate determination (Anderson 1993), migration, and differentiation (Kalcheim 1996), as well as on cell survival (Grothe and Wewetzer 1996). Starting at the earliest stages of brain development, both FGF-1 and FGF-2 have been shown to be expressed in distinct expression patterns (Eckenstein 1994; Vaccarino et al. 1999; Gremo and Presta 2000), with their expression persisting even in the adult CNS.

The most prominent differences between both factors concern their cellular localization, with FGF-2 being expressed by both neuronal and non-neuronal cells, while FGF-1 is localized predominantly in neurons.

In the adult CNS, FGF-1 is found in neurons of the oculomotor nucleus, the pons, the lateral geniculate nucleus, the reticular formation, the ventral tegmental area, the substantia nigra, the hypothalamus, the thalamus, the medial septum, the diagonal bands of Broca, the magnocellular preoptic area, the nucleus basalis of Meynert, the striatum, the cerebral cortex and the hippocampus (Bean et al. 1991; Stock et al. 1992; Bizon et al. 1996) as well as to motoneurons and sensory ganglia (Elde et al. 1991). Furthermore, based on in situ hybridization, neuronal distribution of FGF-1 mRNA has been suggested to occur in the cerebellum, the locus coeruleus, the hippocampus and the neocortex (Wilcox and Unnerstall 1991).

FGF-2 has been found to be localized not only to neurons but also to glial cells (Eckenstein et al. 1991). FGF-2 mRNA is distributed widely throughout the CNS and has been detected in the medulla oblongata, the pons,

Table 3 Viability and phenotypes of available FGF gene deficient mice. For those FGF knockouts which are not available (*NA*) their predominant expression loci are listed

Gene	Null-mutant	Phenotype	References
FGF-1	Viable	No detectable changes	Miller et al. (2000)
FGF-2	Viable	Mild cardiovascular and skeletal disturbances	Dono et al. (1998)
		Disturbed layering of the cerebral cortex	Zhou et al. (1998)
		Disturbed healing of skin wounds	–
FGF-3	Viable	Disturbed inner ear and tail development	Mansour (1993)
FGF-4	Lethal (E4–5)	Disturbed inner cell mass proliferation	Feldman et al. (1995)
		Defects in limb development	Sun et al. (2002)
FGF-5	Viable	Increased hair growth	Hébert et al. (1994)
FGF-6	Viable	Mild disturbances in muscle regeneration	Fiore et al. (1997, 2000) Floss et al. (1997)
FGF-7	Viable	Disturbed growth of hair follicles	Guo et al. (1996)
		Disturbed growth of ureteric bud	Qiao et al. (1999)
FGF-8	Lethal (E7)	Gastrulation defects	Meyers et al. (1998)
		Defects in CNS (mid-hindbrain boundary)	Reifers et al. (1998)
		Defects in limb development	Sun et al. (1999) Sun et al. (2002) Shanmugalingam et al. (2000)
FGF-9	Lethal (P0)	Functional lung deficits	Colvin et al. (2001a, 2001b)
		XY sex reversal	
FGF-10	Lethal (P10)	Developmental defects of lung, limb, thymus and pituitary	Ohuchi et al. (2000) Min et al. (1998)
		Disturbed development of external genitalia	Sekine et al. (1999)
		Disturbed skin formation	Haraguchi et al. (2000) Suzuki et al. (2000)
FGF-11	NA	Expression in neuronal precursor cells	Luo et al. (2002)
FGF-12	Viable	Disturbed neuromuscular functions	Ornitz and Itoh (2001)
FGF-13	NA	Expression in the developing nervous system	Hartung et al. (1997)
FGF-14	Viable	Neurological defects leading to ataxia and paroxysmal dyskinesia	Wang et al. (2002)
FGF-15	Lethal (E9.5)	Unknown	McWhirter et al. (1997)
FGF-16	NA	Growth of brown adipocytes	Konishi et al. (2000)
FGF-17	Viable	Disturbed cerebellar development	Xu et al. (2000)
FGF-18	Lethal (P0)	Skeletal defects	Ohbayashi et al. (2002)
FGF-19	NA	Transgenes show higher energy expenditure and thereby a reduced risk for obesity and diabetes	Tomlinson et al. (2002)
FGF-20	NA	Expression during bone and limb development	Hajihosseini and Heath (2002)
FGF-21	NA	Predominantly expressed in liver and thymus	Nishimura et al. (2000)
FGF-22	NA	Predominant expression in the inner root sheath of the hair follicle	Nakatake et al. (2001)
FGF-23	NA	Predominant expression in the brain (ventrolateral thalamic nucleus) and in the thymus	Yamashita et al. (2000)

the colliculi, the thalamus, the olfactory bulb, and the cerebral cortex (Ernfors et al. 1990). Another study revealed that FGF-2 is located in neurons of the cortex, the hippocampus (Gomez-Pinilla et al. 1994), the substantia nigra as well as in striatum (Bean et al. 1991) and brainstem (Grothe and Janet 1995). Furthermore, FGF-2 has been found to be present in motor and sensory nuclei (Grothe et al. 1991) as well as in the neural and anterior lobes of the pituitary (Gonzalez et al. 1994).

In the adult CNS, also the different subtypes of FGF receptors are known to be expressed. FGFR-1, FGFR-2 and FGFR-3 are found to be highly expressed in the diencephalon and telencephalon and moderately expressed in the mesencephalon and metencephalon, while expression of these FGF receptors is relatively low in the myelencephalon (Belluardo et al. 1997). FGFR-1 is expressed in the widespread but specific neuronal populations in the adult CNS (Asai et al. 1993; Yazaki et al. 1994), but has also been detected in astrocytes of white matter tracts (Takami et al. 1998).

In contrast to FGFR-1, which is predominantly expressed on neurons, FGFR-2 is found primarily on glial cells (Asai et al. 1993) as well as FGFR-3 (Yazaki et al. 1994; Miyake et al. 1996).

The fourth member of the FGF receptors (FGFR-4), however, is reported to be strongly expressed only during early stages of development, and apart from one small region (the lateral habenular nucleus) is not detectable in adult CNS (Fuhrmann et al. 1999).

Neurogenesis and differentiation

Actions of FGF family members on neuron differentiation greatly depend on the developmental time point at which a factor is applied. Along this line, it has been shown in vitro that at an early developmental time point FGF-2 is

able to expand the period of dopamine precursor division in conjunction with a delay in differentiation (Bouvier and Mytilineou 1995). In detail, Bouvier and Mytilineou have demonstrated that FGF-2 can expand the period of dopamine precursor division at least until day 8 in culture, which is well beyond the normal division of these cells. This increase in cell division was accompanied by a delay in differentiation as compared to untreated control cultures. Interestingly, Bouvier and Mytilineou observed, upon differentiation, that the high-affinity dopamine uptake values in FGF-2 treated cultures were 20 times maximal control values.

Proliferation stimulating effects of FGF-2 are apparently not restricted to dopaminergic neurons, but have been described for GABAergic neurons as well. However, in this case addition of FGF-2 at a later time-point does not stimulate proliferation (Deloulme et al. 1991).

Restrictions in neuronal fate occur during the transition from a multipotential to a postmitotic cell. This and later steps in neuronal differentiation are determined by extracellular signals. It has been shown that FGF-2 is mitogenic for embryonic spinal cord cells that have already committed to a neuronal pathway and are expressing neuronal phenotypes (Ray and Gage 1994).

In addition, FGF-2 regulates the proliferative fate of striatal mouse stem cells. In cultures of embryonic and adult mouse striatum, insulin-like growth factor (IGF-I) is a key factor in the regulation of neuronal stem cell activation and epidermal growth factor (EGF) and FGF-2 control striatal neuronal stem cell proliferation (Arsenijevic et al. 2001). EGF induces the proliferation of putative stem cells, which give rise to spheres of undifferentiated cells that can generate neurons and astrocytes. These spheres of undifferentiated cells contain FGFR1 mRNA and protein (Vescovi et al. 1993). Exogenous application of FGF-2 regulates the proliferative fate of unipotent (neuronal) and bipotent (neuronal/astroglial) EGF-generated CNS progenitor cells, indicating that sequential actions of growth factors play a role in regulating the generation of neurons and astrocytes in the developing CNS (Vescovi et al. 1993).

Moreover, in the hippocampus, FGF-2 is mitogenic for stem cells and is a differentiation factor for calbindin-expressing hippocampal neurons (Vicario-Abejon et al. 1995). Several studies have shown that FGF-2 is able to influence neurogenesis within the hippocampus (Yoshimura et al. 2001; Palmer et al. 1999; Nakagami et al. 1997). In primary hippocampal cultures, FGF-2 triggers not only phenotypic differentiation, but drives also the formation of neurons of various developmental stages. These different phenotypes include on one hand neurons with precursor and juvenile neuron morphologies which are unable to fire action potentials and, on the other hand, age-matched polarized neurons firing multiple action potentials (Eubanks et al. 1996).

Effects on adult neuronal precursor cells

Proliferation of neural stem cells and differentiation into mature neurons not only occur during development, but can also be detected in the adult brain (Altman and Das 1965). Proliferation of adult neuron precursor cells has been demonstrated for the forebrain in vitro (Alvarez-Buylla and Lois 1995), as well as for the hippocampus and the subventricular zone of the forebrain in vivo (Goldman et al. 1997). An important regulator of prenatal but also of postnatal and adult neurogenesis is FGF-2, which induces proliferation of neural progenitor cells in the hippocampus and in the subventricular zone (Wagner et al. 1999). Subcutaneous injection of FGF-2 at P1 increases [^{3}H]thymidine incorporation by 70% in hippocampal and subventricular zone homogenates and elicits a twofold increase in mitotic nuclei in the dentate gyrus and the dorsolateral subventricular zone, suggesting that FGF-2 penetrates the blood-brain barrier to regulate adult neurogenesis (Wagner et al. 1999).

Cultured hippocampal cells from adult rats are capable of proliferating and generating neurons in defined FGF-2 containing medium, and these cells have been shown to express various neuronal and glial markers, such as O4, NSE, MAP2, NF150, GAD and calretinin. Two months after transplantation to the adult rat hippocampus, descendents of these cells can be found in the dentate gyrus, where they have differentiated into neurons exclusively in the granule cell layer (Gage et al. 1995). An important question is whether progenitor cells, after expansion with FGF-2, exhibit the same degree of plasticity as their primary counterparts, or whether they are more committed to a particular phenotype. In primary cultures of embryonic rat hippocampal progenitor cells, growth under proliferative conditions (due to the presence of FGF-2) was associated with low levels of sodium, calcium, *N*-methyl-D-aspartate (NMDA), and kainate currents as compared to other growth conditions. After multiple passages in the continued presence of FGF-2, sodium, calcium, and NMDA responses declined further, whereas kainate and gamma-aminobutyric acid (GABA) responses remained substantial (Sah et al. 1997). These findings indicate that passaging and growth with FGF-2 yield neuronal precursors that respond to environmental conditions to a much lesser extent than primary cultures.

The striatum is another brain structure where neuronal progenitor cells have been detected (Reynolds et al. 1992; Vescovi et al. 1993). Like in the hippocampus, isolated multipotential progenitors from adult mouse striatum are able to proliferate and differentiate into astrocytes, oligodendrocytes and neuron-like cells under the influence of FGF-2 (Vescovi et al. 1993; Gritti et al. 1996). These neuron-like cells exhibit neuronal electrophysiological properties, and are immunoreactive for GABA, substance P, choline acetyltransferase, and glutamate (Gritti et al. 1996).

FGF-2 was found also to induce cellular proliferative responses in cells cultured from postnatal mouse dorsal root ganglia (DRG; Namaka et al. 2001). After 2 weeks in

serum-free medium containing FGF-2, neurons were rarely observed. However, following removal of FGF-2 and addition of other trophic factors, many differentiated DRG neurons could be identified (Namaka et al. 2001). The requirement for FGF-2 seemed to be confined to distinct developmental time-windows in these cultures. For a subpopulation of DRG neurons (termed P-neurons for their "pear-like" shape), for example, it was shown that they sequentially required first NGF and subsequently FGF-2 for their survival (Acosta et al. 2001).

Postnatal neurogenesis also occurs in the cerebellum. In the neonatal rat cerebellum, a single postnatal injection of FGF-2 elicited mitosis of neuronal precursors in the external granular layer (EGL; Cheng et al. 2001). Moreover, it increased cells, which label for mitosis, by 100% and total cell density by 33% in the internal granular layer (IGL), the final destination of the EGL precursors (Cheng et al. 2001). Together, these data may indicate that FGF-2 can trigger cerebellar neurogenesis. In consequence, a knockout of the FGF-2 gene may be hypothesized to interfere with neuronal development. FGF-2-deficient mice are viable, and display distinct neuronal defects, e.g., a numerical deficit in cortical neurons. The volume of the dorsal cerebral cortical anlage is substantially smaller, whereas the volume of the basal cerebral cortical anlage is unchanged. Furthermore, the dorsal cerebral cortical anlage of FGF-2 knockout mice has fewer founder cells and a reduced expansion of the progenitor pool over the first portion of neurogenesis, and cortical neuron number is strongly decreased in FGF-2 knockout mice by the end of neurogenesis (Raballo et al. 2000).

Axon growth and branching

Besides their effects on proliferation and differentiation of neural precursor cells, FGFs have been found also to affect neuronal morphogenesis. A prominent neuronal morphological differentiation process is the elongation and branching of processes. Many growth factors, e.g., BDNF and NT-4, have been shown to influence axon branching; however, one of the most effective regulators of this process is FGF-2 (Patel and McNamara 1995; Kalil et al. 2000).

Although axon branching of dissociated cortical neurons occurs in the absence of targets, application of a target-derived growth factor, FGF-2, greatly enhances branching (Kalil et al. 2000). Within the hippocampus, multiple factors enhanced branching of axons but not dendrites of these neurons. The most effective factor in axonal branching has been found to be FGF-2, whereby other factors have been shown to be less effective (Patel and McNamara 1995). Within the hippocampus, FGF-2 selectively promotes bifurcation and growth of axonal branches without affecting the elongation rate of primary axons, resulting in increased complexity of axonal trees. This accelerated axonal branch formation in the presence of FGF-2 can be restored to the basal rate following removal of FGF-2, indicating that the action of FGF-2 is reversible and continuous presence of the factor is required for a prolonged effectiveness (Aoyagi et al. 1994).

Studies using cultured cortical neurons have revealed that growth cones pause and enlarge in regions, from which at later time points axon branches develop (Szebenyi et al. 1998). Application of FGF-2 to cultured cortical neurons increased the size of growth cones and slowed growth cone advance, leading to a threefold increase in axon branching. FGF-2 also affects growth cone morphology, promoting rapid growth of filopodia within minutes (Szebenyi et al. 2001). Furthermore, branching was more likely to occur when FGF-2 was applied on or near the growth cone, suggesting that distal regions of the axon are more responsive to FGF-2 than other regions of the axon shaft (Szebenyi et al. 2001). Taken together, FGF-2, at least in the hippocampus and the cortex, can promote axonal branching by enhancing the formation of collateral axon branches. Support for a putative in vivo relevance of these observations comes from studies of an injury model of the entorhinal cortex-hippocampal connection, where denervation of the hippocampal formation induces axonal sprouting, an event which is accompanied by the elevation of various growth factors, including FGF-2 (Ramirez et al. 1999). Along this line, i.v. infusion of FGF-2 into rats with unilateral entorhinal lesions leads to an increase in the sprouting of axon terminals of the cholinergic septodentate pathway (Ramirez et al. 1999). This indicates a role of FGF-2 in the regulation of injury-related axonal remodeling of this cholinergic pathway.

Neuroprotection and lesion repair

Multiple evidence suggests that FGFs are potent trophic factors for many different populations of neurons in vitro and following brain lesions (cf. Bieger and Unsicker 1995). For example, it has been shown in the hippocampus that FGF-2 decreases glutamate induced neuronal cell death by regulating glutamate receptor subunits, leading to a suppression of the 71-kDa NMDA-receptor protein (NMDARP-71) but not of the AMPA/kainate receptor GluR1 (Mattson et al. 1989, 1993). Furthermore, FGF-2 potentiates quisqualate induced inositol phosphate formation in hippocampal cultures from day 1 up to 10 days, and this effect can be blocked by addition of the AMPA/kainate receptor antagonist 6, 7-dinitro-quinoline-2, 3-dione (DNQX), suggesting an involvement of an AMPA/kainate receptor subtype distinct from GluR1 (Blanc et al. 1999). The neuroprotective effects of FGF-2 on glutamate lesioned hippocampal neurons apparently require the presence of additional growth factors in the medium, e.g., glial cell line derived neurotrophic factor (GDNF; Lenhard et al. 2002).

FGF-2 can also promote survival of septal cholinergic (Otto et al. 1989) and non-cholinergic neurons (Cummings et al. 1992) following fimbria-fornix transection.

However, according to an in vitro study by Perkins and Cain (1995), effects of FGF-2 on cholinergic neuron survival seem to be an indirect effect, involving stimulation and expansion of glial cells as a source for "secondary" survival factors (Perkins and Cain 1995). Another neuron population, for which FGF-2 can act as a trophic factor, are mesencephalic dopaminergic neurons. These neurons are also immunoreactive for FGF-2 in vivo and in vitro (Tooyama et al. 1992; Casper et al. 1994). Survival of dopaminergic neurons in cultures from embryonic midbrain exposed to the dopaminotoxic substance 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) or to its active form, the methyl pyridinium ion (MPP^+), was significantly augmented by treatment with FGF-2 (Otto and Unsicker 1993a). Moreover, FGF-2 partially prevents the deleterious chemical and morphological consequences of an MPTP-mediated nigrostriatal lesion in vivo as has been shown by simultaneous FGF-2/MPTP treatment (Otto and Unsicker 1990; Otto and Unsicker1993b). Furthermore, resistance of dopaminergic neurons to L-glutamate mediated toxicity was greatly enhanced in the presence of FGF-2 (Casper and Blum 1995). Together, the current data are strongly indicative of FGF-2 being a potent neuroprotective agent for dopaminergic midbrain neurons. However, the underlying mechanisms are still a matter of debate. Two possibilities have been discussed so far, with the induction of additional growth factors like the TGF-βs by FGF-2 on one hand (Krieglstein et al. 1998), and the regulation of other cellular communication pathways such as gap junctions on the other (Leung et al. 2001). Thus, intact gap-junction communication is required for survival promoting effects of FGF-2 for dopaminergic midbrain neurons (Leung et al. 2001), with a blockade of gap junction communication by oleamide leading to a clear reduction of survival rates of dopaminergic midbrain neurons in the presence of FGF-2.

Another FGF family member able to promote neuron survival to an equivalent extent to FGF-2 is FGF-8. FGF-8 can protect rat hippocampal neurons from oxidative stress as exerted by treatment with hydrogen peroxide (Mark et al. 1999). In a time course study, it has been reported that FGF-8 is neuroprotective when added as a pre-treatment, co-treatment, and even at 2 h postinsult (Mark et al. 1999). This may indicate that FGF-8 is useful in treatment of oxidative insults, such as stroke.

As demonstrated in previous sections, a prominent feature of FGF functions are their neuroprotective effects. Clues for the in vivo relevance of neuroprotective effects of FGFs and for a possible role in lesion repair came from several studies, in which FGF-2 and other FGF family members were shown to be regulated in response to brain damage. As has been demonstrated for cholinergic neurons of the hippocampus (Anderson et al. 1988; Otto et al. 1989) and for dopaminergic nigrostriatal neurons (Otto and Unsicker 1990), FGF-2 is able to prevent neuronal death after fiber transection or chemical injury. In accordance with these findings, endogenous FGF is greatly upregulated after lesioning. Following cortical lesions FGF-2 mRNA and protein are upregulated for up to 2 weeks, with microglia and reactive astrocytes being the primary source of FGF-2 synthesis (Frautschy et al. 1991). Along this line, entorhinal cortex lesions elicit an increase in FGF-2 in the outer molecular layer of the dentate gyrus ipsilateral to the lesion (Gomez-Pinilla et al. 1992). Interestingly, it has been shown that FGF-2 mediated repair processes can also improve behavioral scores of mice after lesioning (Ishihara et al. 1992), indicating a prominent role of FGF-2 in brain repair.

Ischemia

Ischemic insult results in the destruction of distinct brain regions depending on the type of vascular occlusion applied. Hippocampal ischemia has been shown to cause rapid neuronal cell death (Martone et al. 2000; Kirino 2000), which can be overcome by neuroprotective growth factors, including FGF-1, FGF-2 and FGF-7 (Ogata et al. 1996; Nakata et al. 1993; Cuevas et al. 1998; Sadohara et al. 2001). FGF-2 has been shown to be upregulated within the lesioned brain during several lesion paradigms including ischemia (Martinez et al. 2001; Masumara et al. 1996). In animal models of brain ischemia, FGF-1 and FGF-2 have been widely documented to prevent cell death resulting from ischemic damage. Thus, application of FGF-1 into the lateral cerebral ventricles prior to or even shortly after an ischemic insult prevents the death of hippocampal pyramidal cells (Sasaki et al. 1992). Similarly, application of FGF-2 also prevented CA1 neuronal damage in a dose-dependent manner (Nakata et al. 1993). Interestingly, even systemic administration of FGF-2 can ameliorate acute focal ischemic injury in the cerebral cortex without increasing blood flow following occlusion of the middle cerebral artery (MCAO; Bethel et al. 1997). Two hours after MCAO and a 24-h reperfusion interval, FGF-2-like immunoreactivity appeared to be upregulated in both the striatum and the frontoparietal cortex. In the core of the infarct and in the surrounding region, the so-called penumbra, FGF-2 immunoreactivity was mainly located in astrocytes. In addition, some neurons in the penumbra displayed FGF-2 immunoreactivity as well (Wei et al. 2000). Together, these data suggest that FGF-2 is upregulated and can act as a protective factor after focal cerebral ischemia.

Recently, it has been demonstrated that endogenously synthesized FGF-2 is necessary and sufficient to stimulate proliferation and differentiation of neural progenitor cells in the adult hippocampus after brain insult (Yoshimura et al. 2001). In this study the authors demonstrated that in FGF-2 deficient mice BrdU labeling was attenuated after kainic acid or MCAO in the hippocampal formation as compared to wild-type littermates. In conjunction with this, intraventricular injection of a herpes simplex virus-1 amplicon vector carrying the FGF-2 gene into FGF-2–/– mice showed that the number of BrdU-labeled cells was restored to values equivalent to that of wild-type littermates after kainate seizures.

Mechanisms underlying the neuroprotective capacity of FGF-2 are still largely enigmatic. It has been speculated that the neuroprotective effects of FGF-2 result, in part, from a prevention of attenuation of oxidative damage (Zhang et al. 1993). It has also been found that FGF-2 as well as some other factors are effective in suppressing oxidative impairment of synaptic transporter functions, and that FGF-2 suppresses oxidative stress and mitochondrial dysfunction induced by amyloid beta-peptide and Fe^{2+} in synaptosomes (Guo and Mattson 2000).

Seizures and seizure-induced brain damage

It is well established that glutamate plays a major role in mediating acute ischemic neuronal degeneration in the CNS (Rothman and Olney 1986; Kiessling and Gass 1994; Ikonomidou and Turski 1995). Cerebral ischemia is associated with excessive release and extracellular accumulation of glutamate, which leads to persistent activation of glutamate receptors and acute neurotoxic degeneration of the hyperstimulated neuron (Ikonomidou and Turski 1996).

Glutamate mediated neurotoxicity can also be observed in epilepsy (Olney et al. 1986). A model system for brain seizures is the application of kainic acid (kainate) or bicuculline, which are both able to induce seizures and seizure-induced brain damage (Olney et al. 1986). Bicuculline is a $GABA_A$ receptor antagonist, whereas kainic acid acts as an agonist of a specific set of glutamate receptors (kainate receptors; von Bohlen und Halbach and Dermietzel 2002).

Whether FGFs have anticonvulsant or proconvulsant properties is still a matter of debate. On one hand, FGF-2 does not induce major anticonvulsive effects when administered prior to or after kainic acid induced seizures (Liu et al. 1993; Liu and Holmes 1997a). However, FGF-2 has been found to induce seizures on its own after unilateral injection into the dentate gyrus (Liu and Holmes 1997b). In contrast, exogenous application of FGF-1 decreases convulsions in the kainate model (Cuevas and Gimenez-Gallego 1996), indicating that FGF-1 may have anticonvulsant properties. In addition, both FGF-1 (Cuevas et al. 1994) and FGF-2 (Liu et al. 1993) prevent cell loss in the hippocampus, indicating that FGF-2 has a substantial neuroprotective effect in the kainate model. Following kainate-induced seizures, FGF-2 gene expression in the hippocampus is elevated and peaks 24 h after injection of the convulsant (Riva et al. 1994). Likewise, FGF-2 mRNA increases in the bicuculline seizure model (Riva et al. 1992). In both cases most of the FGF-2 was apparently of non-neuronal origin, since kainate induces a marked increase in astroglial, but not neuronal, FGF-2 mRNA. It is conceivable that upregulation of astroglial FGF-2 may result from the excessive release of endogenous glutamate following seizure activity, leading to activation of glutamate receptors on astroglial cells (Humpel et al. 1993).

Glial cells as an important source of FGFs

As mentioned above, glial cells constitute an important source for the synthesis of certain FGF family members in the CNS. In particular, astrocytes are a prominent location for the synthesis and release of FGF-2, expression of which is regulated by different physiological and pathological stimuli. Following oxygen deprivation, a peak of FGF-2 protein expression can be observed in cultured astrocytes 24 h after the onset of ischemia-like conditions (Liu and Zhu 1999). A similar increase in FGF-2 immunoreactivity and a moderate increase in expression of FGFR-1 was also found in astrocytes after serum and glucose deprivation or glutamate treatment (Liu and Zhu 1999).

FGF-2 released by astrocytes is an important stimulus for growth of neuronal cell processes. Thus, it has been shown that the length of axons and dendrites of E18 mouse cerebral cortical neurons is significantly increased in cultures treated with conditioned medium from astrocytes, as compared to neurons incubated with fibroblast conditioned medium (Le and Esquenazi 2002). Further along this line, FGF-2 specific neutralizing antibodies significantly reduced an astrocyte dependent increase in neuronal process growth, whereas heparin, a coactivator of FGFRs, further enhanced process outgrowth (Le and Esquenazi 2002). Regulation of astroglial FGF-2 release seems also to be important for neuron survival and neurite growth. The aminergic neurotransmitter dopamine enhances astroglial release of FGF-2, which in turn is able to promote survival and process formation of tyrosine hydroxylase positive neurons in E14 embryonic midbrain cultures. This effect can be specifically blocked by FGF-2 specific antibodies (Reuss and Unsicker 2000).

In addition to FGF-2, FGF-9 has been detected in glial cells. Nakamura et al. (1999) have demonstrated, by using double immunofluorescence detection and by in situ hybridization, FGF-9 specific signals in GFAP-positive astrocytes in the white matter tracts of the spinal cord and in the brainstem of adult rats. In addition, FGF-9 could be detected in CNPase-positive oligodendrocytes in rat cerebellum and corpus callosum (Nakamura et al. 1999).

Effects of FGFs on glial cell functions

Besides their role as a source for FGF, glial cells are also a prominent target for different FGF family members. Several studies addressing auto-/paracrine actions of FGF-2 on astrocytes have been published, and gap junctions, neurotransmitter sensitivity, and intermediate filament density have been shown to be affected (Gomes et al. 1999; Reuss et al. 1998, 2000a, 2000b). In addition to astrocytes, oligodendrocytes are important target cells for FGF actions. Responsiveness of astrocytes and oligodendroglial cells to FGFs is further supported by the fact that both cell types express the IgIIIc splice variant of FGFR2 and FGFR3 (Miyake et al. 1996; Reuss et al. 2000). Another glial cell type which is affected by

FGFs is microglia (Goddard et al. 2002). Activation of all three glial subpopulations, astrocytes, oligodendrocytes, and microglia, can be observed after injection of FGF-2 in the cerebrospinal fluid (Goddard et al. 2002), resulting in increased GFAP expression, swelling of the cell bodies, and enhanced formation of processes in astrocytes. The same study demonstrates a significant increase in the number of ED1 labeled microglia and a change in microglial morphology towards a multipolar and granular appearance after FGF-2 injections. Finally in oligodendrocytes, a loss of myelin sheaths was observed after injections of FGF-2 (Goddard et al. 2002). As demonstrated by Cohen and Chandross (2000), FGF-2 is not the only FGF family member to influence oligodendrocyte performances, as FGF-9 is able to modulate the expression of myelin related proteins and multiple fibroblast growth factor receptors in developing oligodendrocytes.

In an in vitro study on the effects of FGF-2 and TGF-β1 on astrocytes, these factors have been claimed to act antagonistically on astrocyte differentiation as monitored by GFAP expression (Reilly et al. 1998). In this study, treatment with TGF-β1 led to a significant increase in GFAP mRNA and protein, whereas FGF-2 changed astrocytes from a polygonal to a stellate morphology and suppressed GFAP expression. In addition both factors seemed to interfere with each other since FGF-2 inhibited the TGF-β1-mediated increase in GFAP mRNA and protein. However, suppression of GFAP expression reported by Reilly et al. (1998) was contradictory to earlier reports about FGF-2 dependent induction of GFAP in astrocytes (Perraud et al. 1990; Eclancher et al. 1990).

A special feature of FGF-2 in astrocytes is its subcellular localization during regulation of astrocyte proliferation. As proposed by Stachowiak et al. (1997), astroglial activation leads to nuclear translocation and accumulation of FGF-2 and its receptor. This finding has been confirmed by Joy et al. (1997).

Besides their effects on astrocyte differentiation, FGFs have also been shown to regulate other astroglial cell functions, including gap junction coupling and neurotransmitter sensitivity (Reuss et al. 1998, 2000a, 2000b). In cultured cortical and striatal, but not in mesencephalic, astrocytes, FGF-2 causes a transient time and concentration dependent reduction of connexin43 protein, mRNA, and intercellular communication as revealed by dye spreading (Reuss et al. 1998). Similar effects have been described for FGF-5 and FGF-9, which also downregulate astroglial gap junctions and functional coupling, although with different brain region specificity (Reuss et al. 2000a). Whereas FGF-5 specifically affects mesencephalic astroglial cells without changing coupling of cortical and striatal astroglia, FGF-9 reduces gap junctional coupling in astroglia from cortex, striatum and mesencephalon. However, the region specific effects of different FGFs on astroglial gap junction coupling were not accompanied by regional differences in FGFR expression, since all three astroglial subpopulations express mRNAs for FGFR2 and FGFR3 (Reuss et al. 1998). Another prominent effect of FGF-2 on astroglial functions is its influence on astroglial sensitivity to dopamine. Treatment of astrocytes with FGF-2 leads to an increase in numbers of dopamine-sensitive astrocytes and to an induction of the D1 dopamine receptor (Reuss et al. 2000b).

Learning and memory

A number of studies suggests that neuronal functions of FGFs are not restricted to the injured brain, but are also important in the normal adult brain, especially in processes attributed to learning and memory. Continuous superfusion of in vitro brain slices with FGF-1 has been shown to decrease the basal amplitude of spikes and significantly increase paired-pulse facilitation in the hippocampus (Sasaki et al. 1994). Tetanic stimulation can induce long-term potentiation (LTP). When FGF-1 is continuously applied, tetanic stimulation leads to an enhancement of the magnitude of short-term potentiation after the tetanus and facilitates the generation of long-term potentiation. Furthermore, FGF-1 also enhances dose dependently post-tetanic potentiation directly after the tetanus (Sasaki et al. 1994). This suggests that FGF-1 may be involved in mechanisms related to the generation of LTP. Since LTP is thought to be linked to memory formation and learning (Bliss and Collingridge 1993), FGF-1 might have a role in mechanisms underlying learning and memory. Evidence supporting this view came from a study using i.c.v. injections of FGF-1. LTP can be induced using a subthreshold stimulation in combination with administration of FGF-1; however, LTP cannot be induced using the subthreshold stimulation alone (Hisajima et al. 1992). Further evidence came from a study using an FGF-1 fragment analog (amino acid residues 1 through 29 of FGF-1 with an alanine substituted at position 16) on accelerated senescence-prone mice. Subcutaneous injection of this FGF-1 fragment analog was found to prolong the mean retention latency and to shorten the latency in a passive avoidance test. In addition, improved performance was also obtained in several other behavioral tests, indicating a beneficial effect of the FGF-1 fragment analog on learning and memory in accelerated senescence-prone mice (Sasaki et al. 1999).

In addition to FGF-1, FGF-2 seems to be involved in neuronal signaling. In the dentate gyrus, subthreshold stimulation (20 pulses at 60 Hz) normally fails to induce LTP; however, after administration of FGF-2, LTP can be induced using this protocol (Ishiyama et al. 1991). A similar model system demonstrating growth factor effects on LTP is provided by the following example: Transection of the fimbria-fornix pathway decreases the frequency of LTP generation. Intracerebroventricular injection of epidermal growth factor (EGF) or FGF-2 facilitated LTP generation in the fimbria-fornix lesioned rats, suggesting that EGF and FGF-2 can improve hippocampal LTP impairment after loss of subcortical afferents (Abe et al. 1992).

Conclusions

The present review has provided an introduction to the structure and functions of the FGF-signaling system in general, and has placed special emphasis on the role of FGFs in brain development, maintenance, and repair processes. The great diversity of effects generated by FGFs is the result of a great diversity of ligands, receptors, receptor splice variants, as well as intracellular messenger cascades that eventually lead to alterations in gene expression. In the CNS at least ten FGF family members are present, but, with the exception of FGF-1 and FGF-2, comparably little is known about their functions, still leaving major gaps in our knowledge about their topographic localization, their gene regulation and their physiological and pathological functions in the brain. Functions known to be regulated by FGFs during development include neurogenesis, axonal branching, and differentiation. However, little is known concerning the role of the different receptor subtypes for these events. Careful analysis of CNS phenotypes of FGF and FGF receptor knockout mice, conditional and cell-specific, are expected to provide more insight into the roles played by FGFs in the brain.

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