Abstract In the peripheral nervous system regeneration and gradual functional restoration occur following peripheral nerve injury. Growth of regenerating axons depends on the presence of diffusible neurotrophic factors, in addition to the substratum. Neurotrophic factors that are involved in peripheral nerve regeneration include nerve growth factor, brain-derived neurotrophic factor, ciliary neurotrophic factor, glial cell line-derived neurotrophic factor, and interleukin-6. Recent functional and expression studies of basic fibroblast growth factor and its receptors have emphasized a physiological role of these molecules in the peripheral nervous system. Basic fibroblast growth factor and its receptors are constitutively expressed in dorsal root ganglia and the peripheral nerve. These molecules display an upregulation in dorsal root ganglia and in the proximal and distal nerve stumps following peripheral nerve injury. In the ganglia these molecules show a mainly neuronal expression, whereas at the lesion site of the nerve, Schwann cells and invading macrophages represent the main cellular sources of basic fibroblast growth factor and the receptors 1–3. Exogenously applied basic fibroblast growth factor mediates rescue effects on injured sensory neurons and supports neurite outgrowth of transected nerves. Regarding the expression pattern and the effects after exogenous administration of basic fibroblast growth factor, this molecule seems to play a physiological role during nerve regeneration. Thus, basic fibroblast growth factor could be a promising candidate to contribute to the development of new therapeutic strategies for the treatment of peripheral nerve injuries.

Keywords Nerve injury · Schwann cell proliferation · Neurotrophic factor · Sciatic nerve · Dorsal root ganglion

Introduction

Adult mammalian peripheral nerves are capable of regenerating and regaining gradual functional restoration after peripheral nerve lesion, in contrast to the central nervous system. This ability is due to the intrinsic regenerative capacity of peripheral axons and, in addition, to the permissive environment for growing axons provided by Schwann cells and extracellular matrix. The cellular events that occur during nerve regeneration are well-known. The changes include leukocytic infiltration at the lesion site and the proximal and distal nerve stump. During the Wallerian degeneration, removal (and recycling) of necrotic tissue and myelin debris at the wound and the degenerating distal nerve stump occurs by macrophages and also by Schwann cells (Fawcett and Keynes 1990). From the proximal nerve stump proliferation of epineurial fibroblasts and blood vessels and of endoneurial Schwann cells takes place (Ramon y Cajal 1928). Axonal growth cones then elongate along the bands of Büngner which are formed by the proliferating Schwann cells. Subsequently, Schwann cells start the process of remyelination (Liu 1981). The neuronal cell body also reacts to nerve injury. The affected perikarya can be identified by the chromatolytic reaction that includes swelling of cell bodies, eccentric nucleus position, and dissolution of the Nissl substance (stained rough endoplasmic reticulum). During the period of chromatolysis, which lasts for 1–3 weeks, massive protein synthesis necessary for regeneration occurs (Lieberman 1971).

In contrast to our knowledge of the cellular changes during peripheral nerve repair, we are only beginning to understand the molecular mechanisms that are responsible for a successful nerve restoration.

The ability and the dynamic of growing axons is not only influenced by the growth substratum like, for example, L1/Ng-CAM and NCAM (Martini and Schachner...
1988; Seilheimer and Schachner 1988) but depends also on the presence of diffusible neurotrophic factors. Neurotrophic factors are molecules that are involved in the development and regeneration of the nervous system. These factors can affect cell survival, transmitter metabolism, synthesis of cytoskeletal proteins and cell surface glycopolymers (for review, see Raivich and Kreutzberg 1993). Neurotrophic factors can be synthesized by the target tissue, but also by surrounding glial cells or the neuron itself (Korsching 1993). Thus, these molecules mediate their effects via receptor-mediated uptake and specific retrograde transport or via an autocrine or paracrine mechanism. Neurotrophic factors are acting via high-affinity receptors; in many cases these are tyrosine transmembrane receptors (Yancopoulos et al. 1990). The prototype and best-studied neurotrophic factor is nerve growth factor (NGF), which belongs to the family of neurotrophins (NT) including, in addition to NGF, brain-derived neurotrophic factor, NT-3 and NT-4/5. Functions of these family members are in part overlapping but also, with respect to the responsive neuron populations, distinct (Lewin 1996; Davies 1997). In addition to the neurotrophins, other neurotrophic factors, like ciliary neurotrophic factor (CNTF; Sendtner et al. 1992), glial cell line-derived neurotrophic factor (GDNF; Hammarberg et al. 1996; Honda et al. 1999; Hoke et al. 2000) and interleukin-6 (Bolin et al. 1995; Gadient and Otten, 1996; Grothe et al. 2000a) are characterized also with regard to their expression and/or function in the peripheral nervous system. Recent functional and expression studies of basic fibroblast growth factor (FGF-2) and its receptors have emphasized a physiological role of this molecule in the developing and regenerating peripheral nervous system. In this review we want to focus on the expression and regulation of the endogenous FGF-2 system in the developing, intact, and injured peripheral nervous system. Furthermore, we summarize the functions of exogenously applied FGF-2 in animal models. Finally, we give an outlook regarding the therapeutic perspectives of FGF-2 for injured peripheral nerves in humans.

**Basic fibroblast growth factor**

FGF-2 is a member of the FGF family, which comprises up to now 23 members (Ornitz and Itoh 2001). FGFs promote mitogenesis of mesoderm- and neuroectoderm-derived cells and are involved in regulating diverse processes like proliferation and differentiation during embryonic development and mediate effects in the adult organism on maintenance and during tissue repair (Böhlen, 1989). In the central nervous system, FGF-2 is found to be expressed in glial cells and distinct neuronal populations (Gonzalez et al. 1995; Grothe et al. 1991; Huber et al. 1997). Regarding the activities, FGF-2 stimulates mitogenesis and differentiation of neuronal precursors and glial cells (Ray et al. 1997) and mediates neurotrophic and neurite outgrowth effects in the injured central nervous system (Grothe and Wewetzer 1996; Grothe et al. 1999).

Mediation of the molecular signals of FGFs occur via two types of binding sites, the low-affinity binding sites represented by heparan sulfate proteoglycans (McKeehan et al. 1998) and the high-affinity tyrosine transmembrane receptors (FGF receptors, FGFR). The FGFR are encoded by distinct genes and, with the exception of FGFR4, display different splice variants by differential splicing (Jaye et al. 1992; Klagsbrun and Baird 1991). Alternative splicing can regulate the ligand-binding specificity (Miki et al. 1992), and the FGFs bind with distinct affinities to the different FGFR (Ornitz et al. 1996). FGF-2, for example, binds to all four receptors, however, with distinct affinities (Ornitz et al. 1996). The highest mitogenic activity of FGF-2 was mediated via the FGFR 1c, 3c and 4, whereas lower mitogenic activity was mediated via FGFR 1b and 2c; FGFR 3b and FGFR 2b revealed no or very few affinities for FGF-2 (Ornitz et al. 1996).

The FGF-2 protein is expressed in different isoforms that display a tissue- and species-specific regulation in cytosolic and nuclear fractions. The isoforms represent different translation products from a single mRNA (Florkiewicz et al. 1991; Florkiewicz and Sommer, 1989). The 18-kDa FGF-2 is initiated at the AUG codon, generation of the higher molecular weight isoforms (21 kDa, 23 kDa) occurs at alternate CUG codons (Florkiewicz and Sommer 1989). During recent years in vitro and in vivo studies have shown that the FGF-2 isoforms are differentially regulated during development and after hormonal stimuli (Giordano et al. 1992; Meisinger et al. 1996; Meisinger and Grothe, 1997b). In addition, as will be discussed below, peripheral nerve lesion also results in differential increase of the FGF-2 isoforms (Meisinger and Grothe 1997a; Grothe et al. 2000a).

**Effects of exogenous FGF-2**

To analyze the protective and restorative effects of exogenously applied FGF-2 in the peripheral nervous system, studies were performed in the adult rat following axotomy of the sciatic nerve. Pharmaceutical application of FGF-2 to the transected proximal nerve stump revealed a prevention of the lesion-induced death of sensory neurons in the dorsal root ganglia (DRG; Otto et al. 1987). In addition, at the lesion site FGF-2 promoted neurite extension and vascularization of the regenerating nerve fibers crossing the gap between the proximal and distal stumps of the disconnected sciatic nerve (Danielsen et al. 1988; Aebischer et al. 1989). Although exogenously applied FGF-2 mediates neurotrophic effects on lesioned peripheral nerves, suggestions about possible physiological relevance are worthless without knowledge of the expression and possible regulation of this molecule in the intact and regenerating peripheral nervous system.