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# The facial nerve axotomy model

Linda B. Moran, Manuel B. Graeber*

*Department of Neuropathology, Division of Neuroscience and Psychological Medicine, Faculty of Medicine, Imperial College London, Charing Cross Campus, Fulham Palace Road, London W6 8RF, UK*

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**Abstract**

Experimental models such as the facial nerve axotomy paradigm in rodents allow the systematic and detailed study of the response of neurones and their microenvironment to various types of challenges. Well-studied experimental examples include peripheral nerve trauma, the retrograde axonal transport of neurotoxins and locally enhanced inflammation following the induction of experimental autoimmune encephalomyelitis in combination with axotomy. These studies have led to novel insights into the regeneration programme of the motoneurone, the role of microglia and astrocytes in synaptic plasticity and the biology of glial cells. Importantly, many of the findings obtained have proven to be valid in other functional systems and even across species barriers. In particular, microglial expression of major histocompatibility complex molecules has been found to occur in response to various types of neuronal damage and is now regarded as a characteristic component of ''glial inflammation''. It is found in the context of numerous neurodegenerative disorders including Parkinson's and Alzheimer's disease. The detachment of afferent axonal endings from the surface membrane of regenerating motoneurones and their subsequent displacement by microglia (''synaptic stripping'') and long-lasting insulation by astrocytes have also been confirmed in humans. The medical implications of these findings are significant. Also, the facial nerve system of rats and mice has become the best studied and most widely used test system for the evaluation of neurotrophic factors.


*Theme:* Development and regeneration
*Topic:* Regeneration

*Keywords:* Axotomy; Glial reaction; Gene expression; Adult; Neonate; Motoneurones; Regeneration; Trophic factors

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* Corresponding author. Tel.: +44-20-8846-7342; fax: +44-20-8846-7794.
*E-mail address:* m.graeber@imperial.ac.uk (M.B. Graeber).
*URL:* http://www.imperial.ac.uk.

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## 1. Introduction

The central nervous system (CNS) is very sensitive to traumatic injury and its capacity to regenerate is limited. Therefore, in the majority of cases, there is no or only incomplete repair following an insult causing delayed restoration and long-lasting or even persistent malfunction. In order to understand better the mechanisms and limitations of CNS regeneration, deeper insights into the cellular and molecular factors that govern the response of both neurones and glial cells to injury are required. However, studies on human subjects are only possible to a very limited extent so that animal models, which faithfully mirror the neurobiological system properties are invaluable tools in the study of the in vivo response of neurones to trauma, providing a means for identifying targets of therapeutic intervention.

Georg Kreutzberg [152] and co-workers popularised the facial nerve axotomy model as a prototypical experimental paradigm for the systematic study of nerve regeneration and degeneration [87,89,91,93,104,131,143,253,274,276,296,322]. As a result of these studies, the model has become the best established in vivo system for the evaluation of neurotrophic factors (Table 1). Therefore, the term "Kreutzberg model" [97] has been proposed for the facial nerve axotomy paradigm.

## 2. Clinical aspects

In man, the *nervus facialis* innervates the muscles that control face expression and thus is of great importance for social interactions. It is the most liable of all the cranial nerves to damage [56,62]. This is in part due to its long anatomical course in the cranium and its rather superficial location after its exit from the skull, which renders facial nerve palsy a common clinical problem. Trauma to the facial nerve commonly occurs as a sequella of road traffic-accidents, as a result of intracranial compression from tumour growth, consequential to infectious diseases or due to damage during surgical manipulations. Facial nerve injury can

Table 1
Effects of growth factors and neurotrophins on facial motoneurone survival

| Neurotrophic/growth factor | Abbreviation | Species | Neonate | Adult | References |
|---|---|---|---|---|---|
| Glial cell line-derived neurotrophic factor | GDNF | Mouse | | ↑ | [118] |
| | | Rat | ↑ | | [20,21,183,231,336] |
| | | Rat | ↑ | ↑ | [329] |
| | | Rat | | ↑ | [242,243,318] |
| | | Rat | ↑ | | [109] |
| Brain-derived growth factor | BDNF | Rat | | ↑ | [140,243] |
| | | Rat | ↑ | | [20,99,146,231,255,316] |
| | | Rat | ↑ | | [328] |
| Neurotrophin 3 | NT3 | | Limited effect | | [69,255] |
| Neurotrophin 4/5 | NT4/5 | Rat | ↑ | | [120,147] |
| Ciliary-derived neurotrophic factor | CNTF | Rat | | ↑ (NR) | [106] |
| | | | | No effect | [243] |
| | | Rat | ↑ | | [20,63,99,254,286] |
| | | *pmn* mouse | | ↑ | [259] |
| | | | ↑ | | [256] |
| | | | ↑ (12–16 days) | | [238] |
| Leukaemia inhibitory factor | LIF | Rat | ↑ | | [120] |
| | | Rat | | ↑ | [106] |
| Basic fibroblast growth factor | bFGF | Guinea pig | | ↑ | [45] |
| Acidic fibroblast growth factor | aFGF | Rat | ↑ | | [55] |
| Recombinant human insulin-like growth factor | rhIGF-1 | Rodents | ↑ | | [315] |
| Insulin-like growth factor | IGF-1 | Rat | ↑ | | [120] |
| | | | | No effect | [243] |
| Cardiotrophin-1 | CT1 | Rat | | No effect | [243] |
| Transforming growth factor-β1 | TGF-β1 | Rat | | ↑ | [136] |
| Transforming growth factor-β2 | TGF-β2 | Rat | | ↑ | [243] |
| Nerve growth factor | NGF | Mouse | No effect | No effect | [291] |
| Platelet factor 4 | PF4 | Guinea pig | | Inhibits (NR) | [45] |

NR: nerve regeneration.

prove to be very debilitating as any facial nerve axotomy equals a functional split between the brain and the face [96].

## 3. Experimental virtues of the facial nerve paradigm

The rodent facial nerve model today represents one of the most widely used animal models to study regeneration and degeneration of the nervous system in vivo [98]. This is due to the fact that the system (Fig. 1) has a number of obvious benefits. The first, the physical distance between the actual site of injury, the stylomastoid foramen and the motoneurone nuclei in the brainstem consists in the fact that there is no direct CNS trauma, no disruption of the blood–brain barrier, and no 'contamination' to any significant extent of the nerve nucleus by an influx of blood-borne elements

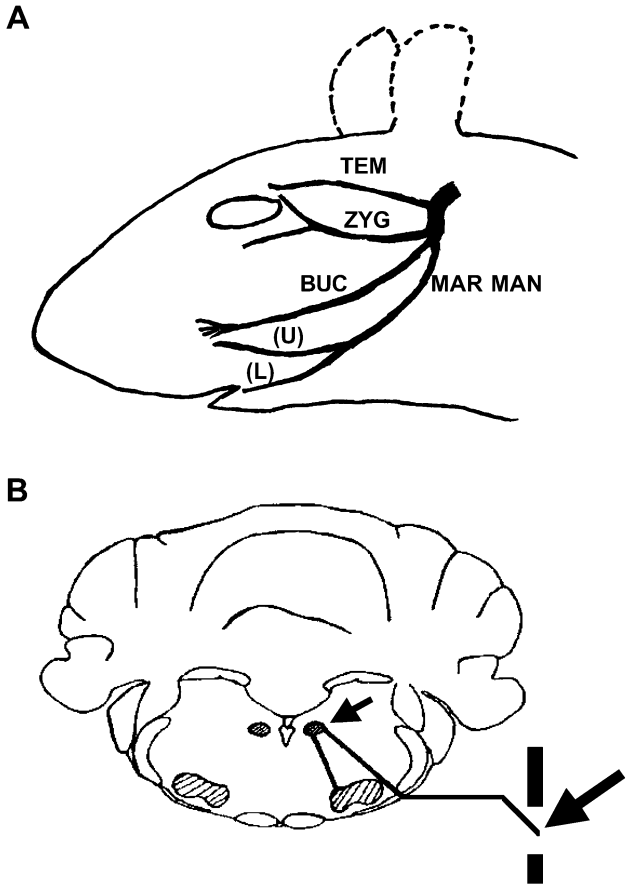


Fig. 1. Schematic diagram of facial nerve innervation and illustration of the axotomy model. (A) Sketch showing the primary branching of the facial nerve of the rat distal to the stylomastoid foramen (modified after Ref. [251]). TEM: temporal, ZYG: zygomatic, BUC: buccal, MAR MAN: marginal mandibular, (U): upper division, (L): lower division. (B) Diagram showing the location of the facial nuclei on either side of the brain stem (hatched areas). The line indicates the trajectory of the facial nerve from the facial motoneurones around the abducens nucleus (genu, small arrow) and finally exiting the boney part of the skull. The facial nerve is transected after its exit from the stylomastoid foramen (large arrow) (modified after Ref. [13]).

Table 2
Facial nerve experimental models

| Type of injury | | Neonatal | Adult | Reference |
|---|---|---|---|---|
| Surgical | Transection | | | |
| | | Hamster | Hamster | [208] |
| | | | Rat | [91,180,191,267] |
| | | Rat | Rat | [3] |
| | | Rat | | [21,289,300] |
| | | | Mouse | [302,303,304] |
| | | Mouse | | |
| | Transection and suture | | Rat | [8,101] |
| | Crush | | Mouse | [302,303] |
| | | Rat | | [21] |
| | | | Rat | [267] |
| | | Rat | Rat | [268] |
| | | Rabbits | Rat/mouse | [304] |
| | Compression | | Rat | [236,326] |
| | Avulsion | Rabbit | Rat | [304] |
| | | | Rat | [237,267] |
| | | Rabbit | | [301] |
| | Resection | | Rat | [7,8,101,191,334] |
| Pharmacological | | | | |
| Toxins | Ricin | | Rat | [189,191,274,275] |
| | Cholera toxin B-saporin | | Rat | [172] |
| EAE | | | Rat | [75,214] |
| FasL | | | Rat | [74] |
| Axonal transport disruption | Colchicine | | Rat | [203] |
| Chemokine | Fractalkine | | Rat | [108] |

[274]. In addition, the surgical procedure is straightforward and of mild severity compared to other models of nerve injury as the nerve consists purely of motor fibres at the height of the lesion site. Researchers further benefit from the analytical strength of a paired experimental system with the normal control nucleus conveniently located on the other side of the brain stem.

For laboratory purposes, the facial nerve axotomy model represents several experimental systems in one. Thus, facial nerve lesions of varying degrees of severity have been used to examine in detail the quantitative and qualitative differences of motoneuronal response patterns and those of their microenvironment following a range of sublethal and lethal stimuli (Table 2). Nerve crush injury, the mildest form of lesion, allows reinnervation to take place as early as 2–3 weeks after the injury [68,171,267,285]. Sheer nerve transection and nerve transection combined with ligation represent more severe challenges eliciting a motoneuronal response, and nerve avulsion with neurectomy is the strongest trigger for neuronal cell death apart from the retrograde transport of toxins such as ricin [56,94,126,187,242,243,267,274]. Accordingly, neurotmesis and axonotmesis of the peripheral nerves have their neuropathological correlates in the facial motor nucleus. Most rodent facial motoneurones survive a simple nerve cut (more so in rats than in mice),

but, as a general rule, a peripheral nerve lesion is more likely to result in neuronal cell death if it is located closer to the nerve cell body [56]. There are significant differences between species [44,163,164,171,268].

A peculiar feature of the lesion response of the facial nerve system in adult *mice* is the site-directed influx of activated T lymphocytes during the late stages of neuronal degeneration [227]. The infiltration of the central facial nucleus by these T cells occurs in the presence of an essentially intact blood–brain barrier. Activated microglia which express high levels of major histocompatibility complex (MHC) classes I and II molecules [227,274–276], and engage in phagocytosis appear to function as antigen-presenting cells [57,77] under this condition. The T-cell infiltration of the facial nucleus of mice following axotomy contrasts with that in axotomised adult rats where T-cell infiltration is not usually apparent. It has been speculated that this remarkable species difference is mainly due to the very low rate of neuronal cell death in the adult rat model [95,274]. A recent study demonstrated that vaccination of adult mice with copolymer-1 (Cop-1, Copaxone), which activates the protective T-cell-mediated response, improves motoneuronal survival and whisker function when compared to non-immunised controls [9]. Proinflammatory cytokines, including interleukin-1β, tumour necrosis factor-α and interferon-γ, are detectable in the mouse axotomy model and may be key factors in controlling lymphocyte recruitment [227]. IL-6, a multifunctional neurotrophin and cytokine, is also rapidly expressed and may be important in initiating "immune surveillance" following injury [79].

## 4. Anatomical considerations

The facial nucleus is located in the brain stem and is about 1.7 mm long and 1.5 mm wide in the rat [321]. Each nucleus harbours between 3200 and 6500 motoneurones, which are organised in three main columns [321], this variability reflecting both the various methodological approaches adopted to quantify them [7,126,181,188,321] as well as a strain differences [127]. Groups of facial motoneurones innervate the muscles that control the movements of the whiskers in the rat [251] and the facial musculature in humans [115]. However, the motor nerve cells within the facial nucleus are heterogeneous with respect to size and shape, and their topographical arrangements depend on differences in the peripheral supply territories of the peripheral branches of the nerve [307]. In the rat, the topographic map shows an orderly arrangement of these subnuclei, with those motoneurones supplying the rostral muscles located laterally while those innervating caudal muscles located medially [321]. The neurones in the facial motor nuclei reach their adult intranuclear location early during postnatal development [141].

Komiyama et al. [148] have provided details of the anatomical location of the facial subnuclei in the mouse. The most important muscles are discussed here: The nasolabial muscle is represented in several areas in the facial nucleus including the dorsolateral, lateral and dorsal intermediate nuclei. The mentalis muscle is represented in the ventral intermediate columns, and the platysma maps to the dorsomedial part of the dorsal intermediate subnucleus and along the lateral border of the dorsomedial and ventromedial subnucleus. The orbicularis oculi and frontalis muscle are represented in the dorsal portions of the dorsolateral, dorsal intermediate and dorsomedial subnucleus. The rostral and caudal auricular muscles are represented in the dorsomedial and ventromedial subnuclei, respectively. The caudal belly of the digastric muscle is supplied by neurones located in the suprafacial nucleus.

## 5. The regeneration model

Peripheral nerve axotomy causes a complex tissue response in the CNS. This tissue response, which affects the microenvironment of the axotomised motoneurone as well as the affected nerve cell body, manifests itself as structural, metabolic, electrophysiological and molecular alterations of the nerve cell, its dendrites and the neighbouring glia [2,157,170,200,210,296,304]. As early as 1974, Watson [320] reported that structural proteins (e.g., as we now know cytoskeletal proteins) are preferentially synthesised whereas messenger RNAs related to neurotransmitter synthesis are down-regulated following axotomy. A number of other changes in the total RNA, protein contents and levels of protein synthesis have been reported [319] (for review, see Ref. [170]). Unscheduled nuclear DNA synthesis (i.e., DNA repair) and enhanced levels of mitochondrial DNA synthesis have been observed in the regenerating facial nucleus [149]. Cellular energy turnover as indicated by glucose uptake increases in regenerating nerve cells as does enzymatic activity associated with basic cellular functions [156,264,294]. Gene activation of the facial motoneurones and their microenvironment has been demonstrated following phytohaemagglutinin-induced target muscle inflammation; with the expression of nitric oxide synthase (NOS) and cell death repressor gene *bcl-2* by motoneurones and the activation of microglia [179].

### 5.1. The regeneration programme of the motoneurone

Over the last few years, the application of molecular biological methods such as Northern blotting, in situ hybridisation and RT-PCR have allowed the characterisation of the regenerative response of the facial nerve system in great detail. For example, in the adult hamster, an increase in ribosomal RNA transcription is detected within 30 min of facial nerve injury [137], but the initiation of the axon reaction appears to be independent of the retrograde transport properties of the axotomised motoneurone [121]. Axotomy results initially in the up-regulation of immediate–

early genes (e.g., c-*jun* and c-*fos*) (for overview, see Ref. [104,248,332]) and a subsequent expression of genes encoding cytoskeletal (actin and tubulin) as well as growth associated proteins (e.g., GAP-43) [191,193,240]. Increased ornithine decarboxylase activity [294] and de novo expression of interleukin-6 (IL-6) mRNA [135] are observed in the axotomised rat facial nucleus as early as 8 h post-injury, whereas calcitonin gene-related peptide (CGRP) mRNA is first detectable 16 h after the lesion [103]. At the same time, the expression of transmitter metabolism associated-enzymes (i.e., choline acetyltransferase and acetylcholine esterase) and receptor proteins becomes reduced [223,293, 320]. Table 3 documents some of the many changes in gene/protein expression observed in adult and neonatal rodents in response to axotomy of the facial nerve system. For example, in the axotomised adult facial nucleus, both motoneurones and glia show an increased expression of several cell adhesion molecules [143,322,323]. In the motoneurones, β-1 intergrin subunit expression is up-regulated and localised to the growth cones of the axonal sprouts in the periphery [143]. The importance of changes in extracellular matrix adhesivity are demonstrated by transgenic deletion studies using α7 null mice (α7 intergrin subunit) where following facial nerve lesions neurite outgrowth is impaired and target reinnervation is delayed [323]. The fundamental character of these changes is underscored by the finding that motoneurones supplying the sciatic nerve and other cranial nerve cell nuclei, notably the hypoglossal motor nucleus show very similar alterations [175,184,216, 220,223].

In neonates, the information available on changes in gene expression is much more limited. The expression profile of some genes is comparable to the adult response, e.g., increases in the expression of glial fibrillary acidic protein (GFAP) [98,289] and changes in neuronal nicotinic acetylcholine receptor expression [252,333]. Similarly, axotomy in neonatal and adult spinal motoneurones leads to a decrease in the mRNA expression of *N*-methyl-D-aspartate (NMDA) receptor subunits NR1, NR2B and NR2D and NR1 subunit protein [222]. However, in contrast to the adult, a significant decrease in both cerebral blood flow and glucose uptake following axotomy has been reported [124]. The observed differences in gene expression between the adult and neonatal facial nerve system are reflected in the completely different outcome after axotomy. In the adult, there is a regenerative process. However, in the neonatal system, there is massive neuronal degeneration and genes associated with cell death notably apoptosis are expressed (e.g., caspase-3 and Bax) [60,61,311]. In fact, unlike in the adult system, true apoptosis is observed in the axotomised neonatal facial motor nucleus. Axotomy of neonatal rat facial motoneurones further induces a marked increase in expression of apolipoprotein J (or clusterin), a multifunctional glycoprotein known to be involved in complement regulation [289]. However, no changes in neonatal motoneuronal sensitivity to neurotransmitters, for example glutamate agonists (*N*-methyl-D-aspartic acid or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) or vasopressin, shown to affect neuronal membrane excitability and synaptic transmission, have been reported following facial nerve axotomy in Bcl2 overexpressing transgenic mice [1].

### *5.2. Rearrangement of central synapses: a necessary accompaniment of the axonal reaction*

Early studies by Blinzinger and Kreutzberg [24] have demonstrated that in the adult rat perineuronal microglia actively engage in the displacement of detached afferent synaptic boutons from the surface of a regenerating motoneurone. This phenomenon is now widely known as "synaptic stripping" [2,96]. Synaptic terminals are lost from the cell body during the first week post-axotomy [24,43,269], but this process is principally reversible following target reinnervation. It may, however, result in overcompensation, i.e., too many synapses, as observed in adult rat spinal motoneurones [29]. Svensson and Aldskogius [282] provided evidence for the loss of synaptic boutons following axotomy of the hypoglassal motoneurones despite the inhibition of reactive microglia by the intracisternal infusion of an antimitotic drug, cytosine-arabinoside. Following severe lesions, i.e., facial nerve cut in the rat, subsequent astrocytic insulation of the regenerating motoneurones may be long-lasting and constitute a "functional glial scar" [87]. Interestingly, in parallel with the synaptic loss, the expression of PSD-95, a protein located at the post-synaptic density and known to be involved in the regulation of synaptic plasticity and synaptogenesis, becomes down-regulated [39]. PSD-95 levels are gradually restored to normal levels by 4 weeks post-lesion. These findings on the malleability of adult synapses in response to peripheral nerve injury are in line with the ultrastructural observations in axotomised cat spinal motoneurones [43] and the vagal nerve system of the guinea pig [67]. Electrophysiological studies including man have confirmed the regular occurrence of this central deafferentation following axotomy [96,160,204]. As the majority of inputs to the soma of motoneurones are inhibitory in nature, the loss of mainly somatic synaptic inputs is likely to be a main cause for their hyperexcitablity [66]. The impaired recovery of fine muscle movements observed following facial nerve trauma in humans [96,204] seems like a logical consequence of these events.

Only a few studies have detailed changes in synaptic input of neonatal motoneurones following axotomy. In newborn spinal motoneurones of the kitten, dorsal root transection causes degeneration of only a few profiles which contact the motoneurones [53]. Delayed synaptic stripping and less pronounced axonal bouton displacement, when compared to the adult, is reported in a qualitative ultrastructural study of axotomised postnatal day (P) 7 and P10 rat hypoglossal motoneurones [26]. As to the mechanisms by which synaptic inputs are removed

Table 3
Regulated expression of known genes/proteins following facial nerve lesion

| Functional category | Expressed gene | Cell type | Expression | Reference |
|---|---|---|---|---|
| *Up-regulated* | | | | |
| Cell adhesion molecules | ICAM-1 | Glia | ↑ | [322,324] |
| | CD44 | Neurones | ↑ | [131] |
| | α7β1 integrin | Neurones | ↑ | [323] |
| | Integrin subunit β1 | Neurones | ↑ | [143] |
| | Integrin subunits β2, α4, α5, α6, αM and αX | Glia | ↑ | |
| | LFA-1 α and β (CD11 and CD18) | Glia | ↑ | [198] |
| Cell death inhibitors | Protein inhibitor of neurons nitric oxide synthase (PIN) | Neurones | ↑ | [40] |
| Cellular protein folding | Glucose-regulated protein 78 kDa (GRP78) | Neurones | ↑ | [200] |
| Chemoattractant | Monocyte chemoattractant protein (MCP-1) | Neurones, glia | ↑ | [76] |
| | MCP-1 receptor (CCR2) | Glia | No change | |
| Chemokines | Fractalkine receptor (CX3CR1) | Glia | ↑ | [108] |
| | Phospholipase Cα | Facial nucleus | ↑ | [241] |
| Cysteine proteases inhibitors | Cystanin C | Glia | ↑ | [194] |
| Cytokines | IL-6 | Neurones, glia | ↑ | [79,135,142,203,277,278] |
| | IL-1β | Facial nucleus | ↑ | [277,278] |
| | IFN-γ | Neurones | ↑ | [213] |
| | TGF-β1 | Facial nucleus | ↑ | [135,277,278] |
| | Tumour necrosis factor (TNF)-α | Facial nucleus | ↑ minimal | [277,278] |
| Cytoplasmic matrix (enzyme) | 5′ -Nucleotidase | Glia | ↑ | [86,155] |
| Cytoskeleton | GFAP | Glia | ↑ | [85,86,129,289] |
| | Vimentin | Glia | ↑ | [90] |
| | Actin, tubulin | Facial nucleus | ↑ | [295,297] |
| | Tα1 tubulin | Neurones | ↑ | [193,297] |
| Extracellular matrix protein | Thrombospondin (TSP) | Neurones, glia | ↑ | [197] |
| | Urokinase-type plasminogen activator (uPA) | Facial nucleus | ↑ | [205] |
| Growth associated proteins | GAP-43 | Neurones | ↑ | [191,216,240] |
| Growth (axonal) | Choline transporter-like protein 1 (rCTL1) | Neurones | ↑ | [41] |
| Heat shock protein | Heat shock protein 70 (hsp70) | Facial nucleus | ↑ | [207] |
| Intermediate filament | Peripherin | Neurones | ↑ | [73,290] |
| | α-Internexin (NF66) | Neurones | ↑ | [190] |
| Macrophage marker | ED1 | Glia | ↑ | [98] |
| Metabolism (fatty acids) | Stearoyl-coA desaturase (SCD-1) | Neurones | ↑ | [246] |
| Metabolism (iron) | Ferretin light chain | Neurones | ↑ | [246] |
| Microglia activation | Protein tyrosine kinase (PTK) (*fgr*, *hck*, *fak*, *jak-2* and *flk-1*) | Glia | ↑ | [150] |
| | CR3 complement receptors (CR3) | Glia | ↑ | [89] |
| | Peripheral benzodiazepine' binding site (PBBS) | Glia | ↑ | [16] |
| | Major histocompatibility complex (MHC classes I and II) | Glia | ↑ | [98,221,276] |
| | | Facial nucleus | ↑ | [169] |
| Neuropeptides | Galanin | Neurones | ↑ | [239] |
| | | Facial nucleus | ↑ | [32] |
| | Cholecystokinin (CCK) | Neurones | ↑ | [239] |
| | FasL | Neurones | ↑ | [74] |
| | Pituitary adenylate cyclase activating polypeptide (PACAP) | Neurones | ↑ | [11,334] |
| | Vasoactive intestinal peptide (VIP) | Neurones | ↑ | [11] |
| | α-Calcitonin gene-related peptide (α-CGRP) | Neurones | ↑ | [239] |
| | Calcitonin gene-related peptide (CGRP) | Neurones | ↑ | [65,103,105] |
| Neurotransmission | Glutamate transporter (GLT-1) | Glia | ↑ | [173] |
| | Glutamate/aspartate transporter (GLAST/GluT-1) | Glia | ↑ | [327] |
| | NOS | Neurones | ↑ | [330] |
| | Nicotinamide adenine dinucleotide phosphate diaphorase (NADPH-d) | Neurones, glia | ↑ | [40,189] |
| | 8-L-Arginine vasopressin ([Arg8]VP) receptors | Facial nucleus | ↑ | [306] |
| | Vasopressin V(1a) receptor | Neurones | ↑ | [49] |
| Neurokines | Platelet-derived growth factor (PGDF) A-chain | Neurones, glia | ↑ | [111] |
| | Platelet-derived growth factor (PGDF) B-chain | Neurones | ↑ | |
| | PDGFα-receptor | Glia | ↑ | |
| | BDNF | Neurones | ↑ | [144] |

(continued on next page)

Table 3 (*continued*)

| Functional category | Expressed gene | Cell type | Expression | Reference |
|---|---|---|---|---|
| | BDNF receptor trkB | | ↑ | [144] |
| | Leukaemia inhibitory factor receptor β (LIFRβ) | Neurones | ↑ | [106] |
| | Signal transducer and activator of transcription (STAT3) | | ↑ | |
| Primary protein kinase C substrate | Myristoylated alanine-rich C kinase substrate (MARCKS) | Neurones, glia | ↑ | [191] |
| | Myristoylated alanine-rich C kinase substrate-like | | No change | |
| | Vesicle-associated membrane protein (VAMP)-2 and -3 | Neurones | ↑ | [42] |
| Protein translation | Ribosomal proteins S3, S6, S7 | Glia | ↑ | [246] |
| | Ef-2 | Neurones | ↑ | |
| Receptors | Transferrin receptors (TfRs) | Neurones | ↑ | [93,246] |
| | GDNFR-α binding protein (GDNFR-α) | Neurones | ↑ | [33] |
| | c-*ret* receptor tyrosine kinase (c-*ret*) | Neurones | ↑ | |
| | Galanin receptor-1 (GalR1) | Facial nucleus | not detected | [32] |
| | Galanin receptor-2 (GalR2) | Facial nucleus | ↑ | [32] |
| | Platelet-derived growth factor (PGDF) α receptor | Glia | ↑ | [111] |
| | Platelet-derived growth factor (PGDF) β receptor | Neurones | ↑ (weak) | [111] |
| Structural proteins | Connexin-43 | Glia | ↑ | [233] |
| | | Glia | ↑ | [246] |
| Transcription factors | c-jun | Neurones | ↑ | [104,332] |
| | jun-B, 12-*O*-tetradecanoylphorbol-13-acetate-induced sequence (TIS) 11 | Neurones | ↑ | [104] |
| | JAK2, JAK3, STAT1, STAT3, STAT5 | Neurones | ↑ (transient) | [249] |
| | STAT5 | Neurones | ↑ | [246] |
| | c-maf | Neurones | ↑ | [246] |
| | oct2 | Neurones | ↑ | [246] |
| | Apolipoprotein J (ApoJ) | Neurones, glia | ↑ | [289] |
| | Intracellular protein tyrosine phosphatase SHP 1 | Glia | ↑ | [117] |
| | PhosphoCREB | Glia | ↑ | [110] |
| *Down-regulated* | | | | |
| Chemokines | Fractalkine | Neurones | ↓ | [108] |
| | MCSF | Facial nucleus | No change | [277] |
| | Phospholipase Cβ1 | Facial nucleus | ↓ | [241] |
| | Phospholipase Cγ1 | | No change | |
| | Phosphatidylinositol 4-kinase | | ↓ | |
| Cotransporters | $K^+$–$Cl^-$ cotransporter (KCC2) | Neurones | ↓ | [305] |
| | $Na^+$,$K^+$–$2Cl^-$ cotransporter (NKCC1) | Neurones, glia | no change | [305] |
| Extracellular matrix protein | Tenascin-R (TN-R) | Neurones | ↓ | [8] |
| Metal binding protein | Growth inhibitory factor (GIF)/metallothionein (MT)-III | Neurones | ↓ | [332] |
| Neurofilaments | Neurofilament polypeptides (68 and 150 kDa) | Facial nucleus | ↓ | [295] |
| | Neurofilament protein (medium and light) | Neurones | ↓ | [297] |
| Neurokines | CNTF receptor α (CNTFRα) | Neurones | ↓ | [106] |
| Neuropeptides | Pituitary adenylate cyclase activating polypeptide (PACAP) high affinity receptors, $PAC_1$ | Neurones | ↓ | [334] |
| | $VPAC_2$ | | No change | |
| | β-Calcitonin gene-related peptide (β-CGRP) | Neurones | ↓ | [239] |
| Neurotransmission | M2 muscarinic receptors | Facial nucleus | ↓ | [116] |
| | Post-synaptic density-95 (PSD-95) | Neurones | ↓ | [39] |
| | Carboxy-terminal PDZ ligand of nNOS (CAPON) | | ↓ | |
| | Neurodap1 | Neurones | ↓ | [206] |
| | Acetylcholine esterase (AChE) | Neurones | ↓ | [69,313] |
| Primary protein kinase C substrate | Vesicle-associated membrane proteins (VAMP) -1 | Neurones | ↓ | [42] |
| Signal transduction | Phosphatidyl inositol-4-kinase (P4 kinase) | Glia | ↓ | [246] |
| Transcription factors | Activating transcription factor 2 (ATF-2) protein | Neurones | ↓ | [182] |
| | Cytochrome oxidase (COX) | Facial nucleus | ↓ | [313] |
| | Islet-1 | Neurones | ↓ | [114] |
| | Protease-activated/thrombin receptor 1 (PAR1) | Neurones | ↓ | [209] |
| | Protease nexin-1 (PN-1) | | ↓ | |

in response to neonatal axotomy, in one of the few studies, Borke [26] reports that, in hypoglossal axotomised motoneurones, axosomatic synaptic boutons are engulfed by the motoneurone somal membrane.

## 6. The glial response to axotomy

In addition to the facial motoneurones, glial cells in their local microenvironment are activated as a result of a remote injury of the peripheral nerve axons. Both microglia and astrocytes of the facial nucleus are stimulated to react [18,24,34,78,134,138,151,265,319]. An early study by Torvik and Skjoerten [303] highlighted the importance of the severity of the peripheral nerve lesion (nerve crush or transection) with regard to the intensity and duration of the glial reaction surrounding adult mouse facial motoneurones. However, aging does not seem to result in qualitative and quantitative changes in the reactivity of either microglia or astrocytes to facial nerve lesion [122].

### 6.1. Microglia

Nissl [211] was the first to report on the "augmentation" (proliferation) of glial cells in the nucleus of origin of the facial nerve in response to peripheral nerve injury. The identity of the proliferating cells as microglia has been confirmed at the ultrastructural level [91]. Microglial activation is characterized by a series of structural and biochemical changes, which are reminiscent of those seen in macrophages under conditions of tissue inflammation. However, "glial inflammation" as exemplified by microglial expression of MHC class II molecules can principally occur in the absence of any infiltration of peripheral immune cells. This is true for the rat model whereas in mice, as mentioned earlier, immune cells infiltrate the facial nucleus and facial motoneurones degenerate.

Activated microglia up-regulate complement type 3 receptors (C3bi receptors, CR3) [89], newly express MHC antigens (classes I and II) [276], but do not necessarily show signs of phagocytic activity [274]. Following intracranial facial nerve transaction in the adult rat, where up to 75% of motoneurones die [187], the complement cascade is activated [185]. Reactive microglia were found to be immunoreactive for several complement components; C1 is weekly expressed 2 days after axotomy, whereas C1q, C3 and C3d were first detected at 4, 7 and 28 days following lesion [185]. Complement activation is also seen following more distal lesions of the adult rat hypoglossal nucleus [281]. Lopez-Redondo et al. [173] demonstrated that activated microglia, found neighbouring axotomised motoneurones following facial nerve transection in adult rats, express high levels of glutamate transporters (sub-type GLT-1/EAAT2), which may play an important role in glutamate homeostasis and neuroprotection. Facial nerve injury also induces the early expression of β-amyloid precursor protein [15] and vimentin [90] in microglial cells. Furthermore, microglia show a biphasic increase in the mRNA expression of intercellular adhesion molecule-1 (ICAM-1) following facial nerve axotomy in the adult mouse. The phases of expression coincide with the early microglia activation and the subsequent phagocytosis of neuronal debris accompanying axotomy-induced cell death [322]. In addition, reactive microglia of the facial nucleus show changes in their expression of leukocyte function associated-1 antigen (LFA-1) [198] and receptors for macrophage colony-stimulating factor (M-CSF) as well as granulocyte–macrophage colony-stimulating factor (GM-CSF) [225] underlining their potential to participate in CNS immune responses.

The response of microglia following facial nerve injury has been studied in cultures using facial nuclei explants [232] or primary microglia cultures [46,92]. Acutely isolated brain slices from the facial nucleus have been used to investigate the membrane properties of identified, microglia in situ [27]. Video time-lapse recordings of slices of neonatal rat brain stem, which included the axotomised facial motor nucleus, were used to demonstrate two types of microglia activity [244]. One subset of microglial cells, found on the surface of the slice were stationary, developed pseudopodia and engaged in phagocytosis of cell debris. The other phenotype, observed deep within the tissue, were of the amoeboid-type, presenting no pseudopodia and showed the capacity to migrate [244]. By all likelihood, the latter are closer to microglia in in vivo pathological settings, where microglia do not necessarily progress to become classical brain macrophages.

### 6.2. The regeneration–degeneration dichotomy

Microglia are resident brain macrophage precursor cells and if the neurones are lethally injured and degenerate, the microglia engage in phagocytosis of the resulting debris. There is no evidence to indicate that microglia commonly attack neurones. The graded response pattern of the microglia to pathological stimuli rather suggests that microglial activation in vivo is tightly controlled although the responsible molecular mechanisms remain to be defined. Under normal conditions, microglia carry out surveillance functions. They can become activated in response to even subtle changes such as ionic disturbances [80] and can engage in synaptic stripping in the regenerating rat facial nucleus without turning into phagocytes [154] (Fig. 2). Microglia have indeed been shown to exert neuroprotective/neurotrophic influences under certain conditions [273].

Studies employing facial nerve axotomy in the newborn rat demonstrate activation of microglia within 1 [98] or 2 days [289] of the injury. Thereafter, microglia rapidly transform into phagocytes, in parallel with the degeneration process affecting the axotomised newborn motoneurones [98]. Just as previously reported in the adult,

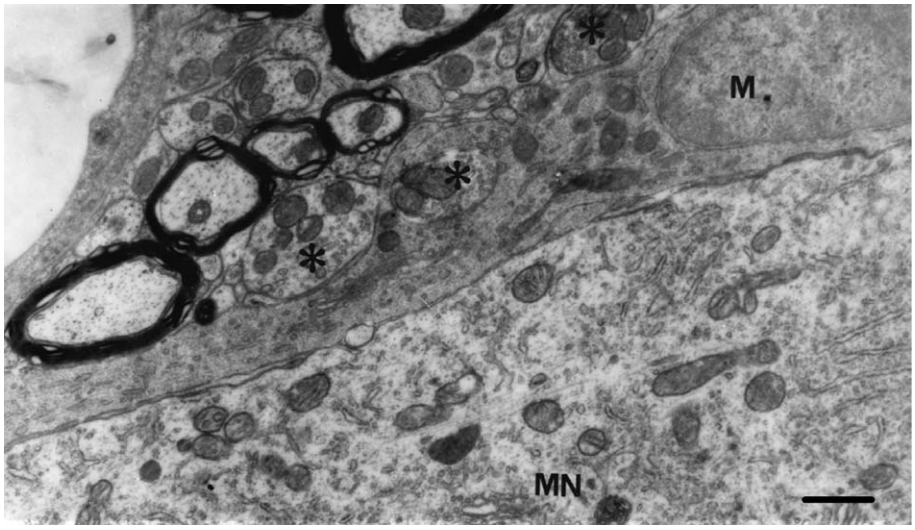


Fig. 2. An electron micrograph of the surface of an axotomised adult motoneurone with a microglia cell engaged in "synaptic stripping". Scale bar 2 μm. The microglia cell (M) is interposed between the motoneurone (MN) soma separating the detached synaptic boutons (*). (Figure courtesy of Professor Georg Kreutzberg).

axotomy of spinal motoneurones induces an increased microglial density around degenerating nerve cells in the cord [201]. Likewise, in newborn rabbits, marked phagocytosis of axotomised facial motoneurones is observed 2–3 days following gentle nerve traction [301]. Torvik [301] commented upon the role of microglial cells in the removal of degenerating neonatal neurones by phagocytosis. Interestingly, there is ultrastructural evidence that axotomy in rat neonatal hypoglossal motoneurones causes a delayed and less intense perineuronal glial reaction when compared to the same lesion in the adult [26]. Interestingly, the phenotypic expression of the glial response is developmental stage-dependent and likely related to the postnatal maturation process of glial cells [26]. It may be of interest to note that complement component C3, known to facilitate phagocytosis by opsonisation, is not expressed in the facial nucleus following facial nerve transection in neonatal rats [289]. Furthermore, a delayed up-regulation of the expression of the complement C3 receptor is observed [289].

### *6.3. The role of astrocytes during regeneration of the facial nerve*

In the adult rodent facial nucleus, concomitant with the proliferation of satellite microglial cells, local astrocytes, which normally express very low levels of the GFAP become reactive and undergo hypertrophy [2,85]. Following the increase in GFAP synthesis, the reactive astrocytes reorganize their cytoskeleton. GFAP is synthesised de novo as early as 24 h after axotomy [296]. However, the overall up-regulation of $mRNA^{GFAP}$ is strongly dependent on the success of neuronal regeneration. Laskawi and Wolff [161] describe differences in GFAP expression by astrocytes in the rat facial nucleus following various types of peripheral nerve lesion. These authors observed a longer-lasting astrocytic reaction following facial nerve transection when regeneration is prevented than following nerve transection and re-anastomosis. In all models (except where the trigeminal branches innervating the vibrissae were transected before the facial nerve), GFAP expression remained elevated for several months post-lesion. Remarkably, 1 year after facial nerve transection when axonal sprouting was impeded, GFAP expression was still higher than in the control nucleus [161]. Interestingly, oral treatment with nimodipine following permanent axotomy of facial and hypoglossal rat motoneurones resulted in prolonged periods of GFAP reactivity and an increase (50%) in the number of astrocytic lamellae surrounding the surviving motoneurones [102].

Little is still known about the signals that lead to the microglia and astrocytes becoming activated following axotomy and the final outcome of this activation. Kiefer et al. [135] reported on the rapid accumulation of IL-6 mRNA as early as 8 h after unilateral facial nerve transaction in the rat, reaching a peak at 24 h. Other proteins such as the astrocytic gap junction protein, connexin-43, become detectable by immunocytochemistry in the ipsilateral facial nucleus of the rat following peripheral nerve axotomy [233]. Connexin-43 expression is focal, confined to astrocytes surrounding lesioned motoneurones and is in keeping with the known intercellular coupling of astrocytes [233]. Reactive astrocytes, present in the adult rodent following facial nerve cut and crush, also show an increased expression of platelet derived growth factor mRNA and protein as early as 3 days following the axotomy [111]. In the hypoglossal nucleus, peripheral nerve injury induces up-regulation of apolipoprotein J in astrocytes ipsilateral to the site of nerve injury [284]. Sciatic nerve transection has been shown to lead to the

expression of NMDA receptors on reactive astrocytes of the spinal cord [223].

In the rat facial nerve model, mitotic cell division is not observed in astrocytes as long as the motoneurones are not lethally injured and survive. Consequently, the appearance of GFAP-immunoreactive astrocytes within the regenerating facial nucleus represents non-mitotic transformation but not proliferation of astrocytes. The hypoglossal nucleus demonstrates the same response pattern [280,283]. Electron microscopy reveals that astrocytic cell processes reshape as a consequence of increased GFAP expression and cytoskeletal reorganisation. The tips of these become thin lamellar cell extensions, which at the end of the second to third week after axotomy begin to take over the perineuronal positions previously occupied by microglia cells [87]. After 3 weeks following the operation, these sheet-like lamellar processes cover virtually all neuronal surface membranes, which have lost their afferent boutons. Subsequently, the lamellar processes become arranged in stacks and persist for several months and may even become permanent if target reinnervation is prevented [86,230,304]. In the spinal cord, astrocytes have also been implicated in the process of synaptic bouton displacement [28]. Ensheathment of the axotomised motoneurone has been suggested to partially depress the synaptic drive from selected afferent inputs, as well as to provide metabolic support [2,4]. Importantly, peripheral reinnervation of the target musculature takes place despite this central deafferentation, in general within 2–3 weeks following crush lesion and by 4 weeks following nerve transection. This illustrates that the motoneurone does not require full restoration of normal afferent synaptic input before regrowing its neurite and reinnervation of the musculature.

The observed long-term deafferentation of the regenerating motoneurones by glial cells is of obvious clinical importance [96]. The delayed astrocyte reaction may serve a protective role by preventing phagocytosis (neuronophagia) by microglial cells. In addition, the astrocytic processes, which cover large areas of the motoneurone soma, may protect vacated post-synaptic sites from being ‘taken-over’ by inappropriate axonal connections. The changes in astrocytes and microglia observed in the facial nucleus in fact represent a very common phenomenon: a high degree of structural neuroplasticity involving glia is also seen in other brain regions and even under physiological conditions where astrocytic multilamellar processes are found to encapsulate neuronal somata and dendrites [153].

In common with the adult response, in the neonatal model, astrocytes respond to facial nerve injury by increasing their expression of GFAP within 1 day of injury [289]. However, in contrast to the adult, astrocytes proliferate following facial nerve axotomy in newborn rats [289]. Both neonatal and adult reactive astrocytes, which surround the axotomised facial motoneurones, up-regulate their expression of apolipoprotein J [289] and, in the neonate, these astrocytes express inducible NOS [36].

## 7. Trophic factors and nerve regeneration

Studies by Sendtner et al. [253] first demonstrated the role of the ciliary neurotrophic factor (CNTF) in motoneuronal survival following its local application to lesioned axons in the newborn rat. Subsequently, other neurotrophic and growth factors were found to prevent axotomy-induced motoneurone cell death including neurotrophin-4/5 (NT-4/5), insulin-like growth factor-1 (IGF-1), leukemia inhibitor factor (LIF) [120], CNTF, brain-derived neurotrophic factor (BDNF) [257], nerve growth factor (NGF) [270] and neurotrophin-3 (NT-3) [167]. Continuously released glial cell line-derived neurotrophic factor (GDNF) by synthetic guidance channels that bridged an 8-mm gap in the facial nerve efficiently promoted axon regeneration in adult rats [17]. Numerous studies have used the facial nerve axotomy model to investigate the survival promoting effects of these neurotrophic and growth factors on axotomised motoneurones (Tables 1 and 4). There is evidence that although these neurotrophic factors can promote regeneration in the facial nerve model, the functional outcome is often limited or remains unchanged [145,196]. In some cases, the motoneurones are not rescued but kept alive transiently despite continuous, local or systemic delivery of the neurotrophic factor [99]. Overall, the clinical hopes raised by the widely publicised work on neurotrophic factors have not been fulfilled.

Several factors are reported to enhance axonal reinnervation of the target musculature following facial nerve injury including insulin-like growth factor-1, basic fibroblast growth factor [45]. Interestingly, polyamines have been shown to accelerate recovery after facial nerve injuries [82], which fits well with the rapid, transient increase in polyamine biosynthesis observed following injury [81,294]. Gonadal steroids, e.g., testosterone propionate (TP) and its metabolite estradiol or dihydrotestosterone, are reported to have a role in promoting axonal regeneration [128,137,288]. Intrinsic sex differences in the abundance, distribution pattern and regulation of androgen receptors are seen in facial motor nuclei [331]. In the hamster facial nerve system, there is evidence that TP enhances the functional recovery and the axonal regeneration rate following crush injuries [158,159] by attenuating the effects of facial nerve transection on GFAP at the mRNA and protein level [51].

The facial nerve axotomy model lends itself well to studies on novel therapeutic approaches to the protection of motoneurones in neurodegenerative diseases. Several neuroprotective agents have been identified including pyrrolopyrimidine PNU-101033-E, which is shown to improve the survival of injured facial motoneurones in the adult rat [186] and nimodipine, a voltage-gated calcium channel antagonist, which improves the time course of functional recovery and axonal regrowth following intracranial axotomy of the facial nerve [188]. In addition, treatment with LSL 60101, a ligand that selectively binds to the $I_2$-imidazoline receptor, which is found on brain glial cells, has a

Table 4
Facial nucleus knock-out/transgenic models

| Type of mutant mouse | Lesion type/age | Response to facial nerve injury | Reference |
|---|---|---|---|
| *Bcl-$x_L$* knock-out | Transection/neonate (P2) | ↑ (50%) Motoneuronal survival (7 dpo) | [218] |
| Bcl-2 (overexpressing Bcl-2 protein) | Transection/neonate (P2) | ↑ Motoneuronal survival (up to 12 wpo)<br>Electrophysiological properties maintained (20 dpo)<br>↓ Cell size but normal ultrastructure (14 dpo)<br>BDNF treatment prevented cell body atrophy (9 mpo) | [1] |
| | Transection/neonate (P2) | No neuronal degeneration (7 dpo)<br>Axon protected up to lesion site<br>GFAP response | [64] |
| *Bax-deficient* (−/−) | Transection/neonate (P1) | 86% survived (7 dpo and 4 wpo)<br>Somatic atrophy but limited glial reaction | [61] |
| *Bax-deficient* (+/−) | | 10% Neurones survived (7 dpo)<br>Neuronal degeneration, replaced by glial (4 wpo) | |
| WAT (NZB-elicited Wobbler (NEW) mutant carrying the human *Bcl-2* transgene) | Transection/neonate (P2) | No motoneuronal loss (7 dpo)<br>Reduced motoneuronal size with a dense appearance | [54] |
| *pmn* mutant and *pmn*/CNTF knock-out | Transection and deflection/4 weeks | | [259] |
| *pmn*/CNTF$^{+/+}$ | | ↑ Motoneuronal survival (57%, 2 wpo) | |
| *pmn*/CNTF$^{+/-}$ | | ↑ Motoneuronal survival (37%, 2 wpo) | |
| *pmn*/CNTF$^{-/-}$ | | No significant difference in survival (14%, 2 wpo) | |
| *Scid* (severe combined immunodeficient, lacking functional T and B lymphocytes) | Transection/8 weeks | ↓ Motoneuronal survival (~ 40%, 4 wpo) | [260,261] |
| Reconstituted *Scid* (splenocytes containing T and B lymphocytes) | | No significant neuronal loss (1–2 wpo)<br>Motoneurone numbers ↓ with survival (~ 30% , 10 wpo) | [260,261] |
| RAG-2 (recombinase-activating gene-2 knock-out (RAG-2 KO), RAG-2 disrupted and prevents T and B cell maturation) | Transection/8 weeks | ↓ Motoneuronal survival (~ 20%, 4 wpo) | [261,262] |
| Reconstituted RAG-2 (splenocytes) | | No significant motoneuronal loss (4 wpo) | [261] |
| CD4 (CD4+ T cell-deficient) | Transection/adult | ↓ Motoneuronal survival (~ 26%, 4 wpo) | [262] |
| CD8 (CD8+ T cell-deficient) | | No motoneuronal loss (4 wpo) | |
| MμMT (B cell-deficient) | | No motoneuronal loss (4 wpo) | |
| Reconstitution CD4 and RAG-2 knock-out (CD4+ T lymphocytes) | | No motoneuronal loss (4 wpo) | |
| Reconstitution RAG-2 knock-out (CD8+ T lymphocytes) | | ↓ Motoneuronal survival (~ 21%, 4 wpo) | |
| Reconstitution RAG-2 knock-out (B lymphocytes) | | ↓ Motoneuronal survival (~ 23%, 4 wpo) | |
| NF-L (neurofilament light protein) knock-out | Crush/2–3 months | Abnormal reinnervation | [335] |
| NF-L$^{(-/-)}$ | | ↓ Numbers of regenerating myelinated axons (< 5% of controls 9 mm distal to crush site, 9 dpo) | |
| NF-L$^{(+/-)}$ | | ~ 10% of regenerating myelinated axons cf. controls | |
| p75 (−/−) (p75 low-affinity neurotrophin receptor knock-out) | Transection/neonate (P1) | ↑ Motoneuronal survival (~ 17%) | [71] |
| | Crush/6–9 weeks | Enhanced functional recovery (25 dpo) | |
| | Transection/6–9 weeks | Whisker movement regained (25 dpo)<br>↑ Motoneuronal survival (~ 17%) | |
| p75$^{NTR}$ ICD transgenic | Transection/adult | ↑ Motoneuronal death (~ 40%, 7 dpo) | [177] |
| p75$^{NTR}$(−/−) knock-out (low-affinity p75 receptor for the neurotrophins p75 $^{NTR}$) | Transection/newborn | Neuronal survival unchanged (21% cf. 17% in control) | [325] |
| p75$^{NTR\,-/-}$ and application of NGF to lesioned nerve | | Significant ↑ (~ 15%) in neuronal survival | |
| p75 null mutant + NGF (1.9 mg/ml) | Resection/7 days | No difference in motoneuronal survival cf. saline treated control (~ 60% at 1 wpo) | [291] |
| NGF/p75$^{(+/+)}$ (overexpress NGF) | Transection/2–3 months | ↑ Motoneuronal survival (25 dpo) | [72] |
| NGF/p75$^{(-/-)}$ (overexpress NGF but carries two mutated p75$^{NTR}$ alleles, no receptor expression) | | ↓ Motoneuronal survival (25 dpo) | |
| SOD1 transgenic (G93A superoxide dismutase, SOD1) | Transection/~ 4 months | Marked gliosis and neuronal degeneration in the unoperated and operated nuclei, >on lesioned side<br>% Cell death similar to control<br>Microglia hypertrophy, intense activation | [178] |

Table 4 (*continued*)

| Type of mutant mouse | Lesion type/age | Response to facial nerve injury | Reference |
|---|---|---|---|
| V12_Ha_Ras (Ras-transgenic (synapsin I Ras-TG)) | Transection/10 weeks | No motoneuronal degeneration | [112] |
| | | Neurones morphologically normal; no shrinkage | |
| NF-L-Cre; STAT3 $^{flox/KO}$ | Transection/4–5 weeks | Pronounced neuronal loss (2 wpo) | [250] |
| | | ↓ Expression of Reg-2 and Bcl-xl (↓ ~ 34%, 2 dpo) | |
| NF-L-Cre; STAT3 $^{flox/KO}$ + CNTF or GDNF | | Rescued ~ 50% of otherwise degenerated motoneurones | |
| Interleukin-6-deficient (IL-$6^{-/-}$) | Crush (30 s)/3–6 months | ↓ Rate of axonal regeneration (↓ 14% for galanin and 12% for calcitonin gene-related peptide expression) | [79] |
| | | No difference in macrophages or granulocytes at the lesion site (4 dpo) | |
| | | No difference in neuronal survival (30 dpo) | |
| | Transection/3–6 months | Decreased recruitment of CD3-positive T lymphocytes and microglia activation (1–4 dpo) | |
| | | ↓ ICAM1, α5β1, α6β1 and MHC I in activated microglia | |
| | | ↓ Density of microglial cells (3 dpo) | |
| α7-Subunit integrin (transgenic deletion α7 integrin subunit) | Crush/6 months | ↓ Axonal elongation (4 dpo, 33–35% ↓ in galanin and calcitonin gene-related peptide expression) | [323] |
| | | Delayed reinnervation (9 dpo—no reinnervation observed although by 21 dpo, reinnervation rate the same as wild-type) | |
| | | No apparent affect on neuroglial response | |
| Caspase-1/interleukin-1β-converting enzyme (ICE knock-out [ICE$^{-/-}$]) | Transection/2 days | No difference in % neuronal death (4, 6 and 11 dpo) | [60] |
| | Transection/14 weeks | Significant ↓ in motoneurone survival (16%, 6 wpo) | |
| Caspase-3 gene deletion (−/−) | Transection/newborn (P0) | ↑ Motoneuronal survival cf. wild-type (3 fold>, 4 dpo) | [311] |
| | | ↑ Motoneuronal survival cf. wild-type (3 fold>, 7 dpo) | |
| Cardiotrophin deletion (*ct-1*$^{-/-}$ region spanning exon 2 and the complete coding region of exon 3) | Transection/4 weeks | ↓ Motoneuronal survival (non-significant, ~ 9%, 14 dpo) | [215] |
| | Transection/3 or 6 months | ↓ Motoneuronal survival (non-significant, 14 dpo) | |
| Tumour necrosis factor receptor-1 (sTNFR1 transgenic; overexpressing soluble form of tumour necrosis factor receptor-1) | Transection/7 days | ↑ (~ 12%) motoneuronal survival (14 dpo) | [292] |
| IFN-γ signalling pathway, STAT4 and STAT6 | Resected (3 mm)/adult | Conspicuous wild-type strain differences, but not involving STAT4 and/or STAT6 | [169] |
| | | Astrocyte activation, β2-microglobulin or MHC class I unaffected | |
| Interleukin-2 wild-type (C57BL/6-IL2$^{+/+}$) | Transection/8–12 weeks | Marked infiltration, in clusters, of CD3+ T cells | [221] |
| Interleukin-2 knock-out (C57BL/6-IL2$^{-/-}$) | | Marked infiltration of CD3+ T cells (two-fold higher levels cf. wild-type littermates, 14 dpo) | |
| | | Lower numbers MHC II-positive microglia cf. wild-type littermates | |
| Cogenic mice with SCID mutation and wild-type gene alleles (C57BL/6*scid*-IL-2$^{+/+}$) | | No CD3+ T cells | |
| | | Phagocytic microglia clusters present | |
| Cogenic mice with SCID mutation and IL2 knock-out (C57BL/6*scid*-IL-2$^{-/-}$) | | No CD3+ T cells | |
| | | Lower numbers of phagocytic microglial clusters (↓ 50% cf. wild-type littermates) | |
| Interleukin 1 receptor type 1 (IL1R1$^{-/-}$) | Transection/2–3 and 3–6 months | ↓ Motoneuronal numbers (6.4%) | [228,229] |
| | | ↓ CD3+ lymphocytes influx (59% 7 dpo, 54% 14 dpo, 31% 21 dpo) | |
| Tumour necrosis factor receptor type 2 (TNFR 2$^{-/-}$) | | ↓ (8.4%) Motoneuronal numbers | |
| | | ↓ CD3+ lymphocytes influx (42% 7 dpo, 44% 14 dpo, 29% 21 dpo) | |

*(continued on next page)*

Table 4 (*continued*)

| Type of mutant mouse | Lesion type/age | Response to facial nerve injury | Reference |
|---|---|---|---|
| Tumour necrosis factor receptor type 1 (TNFR $1^{-/-}$) | | ↑ (3.4%) Motoneuronal numbers | |
| | | No significant difference in CD3+ lymphocytes influx | [228,229] |
| Tumour necrosis factor receptor type1 and 2 (TNFR $1^{-/-}$ and $2^{-/-}$) | | ↓ Numbers of motoneurones (0–29 dpo, 6.1%) | |
| | | ↓ (63%) CD3+ lymphocytes influx<br>Microglial modules devoid of two microglia markers (αXβ2 integrin-activated microglia and IBA1)<br>Microglia transformed to phagocytic macrophages) | |
| Interferon-γ receptor 1 (IFNγR1$^{-/-}$) | | ↑ (3.2%) Motoneuronal numbers<br>20% ↓ in CD3+ lymphocytes influx (non-significant; 7, 14 and 21 dpo) | |
| Osteopetrotic (op/op) [deficiency in biologically active macrophage colony-stimulating factor (M-CSF)] | Transection/3–6 months | ↓ Density of αMβ2-positive microglia (1–4 dpo) | [132] |
| | | ↓ Expression of microglial activation markers (thrombospondin, αMβ2 and α5β1-integrins; 1–4 dpo)<br>Only focal microglia adhesion to motoneurones (3–4 dpo)<br>↓ (60%) CD3-positive T cells numbers<br>Normal induction of induction of microglial TSP, B7.2, αMβ2 and ICAM1 (14 dpo)<br>Expression of neuropeptides, synaptic stripping, neuronal survival and rate of regeneration unaffected | |
| | Transection/3 months | Strong and selective inhibition of microglia proliferation (~ 80% at 2 dpo and ~ 96% at 3 dpo)<br>Post-traumatic activation of adjacent axotomised neurones; reactive astrocytes unaffected | [226] |
| Fas transgenic/mutant (impaired Fas signalling) | Transection/neonate (P3) | | [309] |
| Fas locus *lpr/lpr* | | ↑ (10.9%) Motoneuronal survival (7 dpo) | |
| FADD-DN β-actin-Fas-associated death [1]domain (FADD)-dominant negative (DN) | | ↑ (16.5%) Motoneuronal survival (7 dpo) | |
| CNTF and CNTF/LIF knock-out | | | |
| $CNTF^{-/-}$ | Transection/4 weeks | 90% Motoneuronal survival (not significant; 2 wpo) | [258] |
| $CNTF^{-/-}$/$LIF^{-/-}$ | Transection/4 weeks | 66% Motoneuronal survival (2 wpo) | |
| $CNTF^{-/-}$ | Transection/adult | Altered time course of STAT3 activation | [139] |
| CD 200 (−/−) (0X02) | Transection/adult | (STAT3 signaling delayed by 10–12 h)<br>Dramatic acceleration of microgelia (2 dop) | [113] |

Abbreviations: dpo: days post-operatively, wpo: weeks post-operatively, mpo: months post-operatively.

neuroprotective role in neonatal axotomy-induced models of motoneuronal death [37].

### 7.1. Quantitative aspects of regeneration

Current evidence suggests that the application of neurotrophins, chemical signals (e.g., drugs like diphenylpiperazine and deprenyl [300] and polyamines and aminoguanidine [82]) and electrical currents may all enhance the regenerative process (for review, see Ref. [47]). Like the central responses of motoneurones, the peripheral reinnervation of the target musculature is dependant on the nature of the lesion. Target reinnervation and motoneuronal survival are greater when the epineurium stays intact, i.e., following nerve crush compared with complete transection [133]. Terao et al. [290] report that whisker movements were restored from 2 weeks after a crush lesion of the facial nerve in adult Wistar Louvain rats, with near normal function was regained by 32 days. This contrasts with the response to facial nerve transection, where reinnervation is first observed 2 weeks following axotomy (11.7 ± 6.7%), reaching only 80% (79.5 ± 14.6%) of the control side at 5 weeks post-axotomy [39]. However, the rate of cell death is also higher following facial nerve cut [56]. Intracranial crush injury close to the motoneuronal cell bodies results in delayed reinnervation, which becomes noticeable in the third week post-lesion. Interestingly, Tetzlaff et al. [298] demonstrates that repeated injury (i.e., a conditional crush lesion followed 7 days later by a "test" lesion) results in higher axonal regeneration rates.

The best surgical management approach to maximize functional recovery following facial nerve trauma in man remains controversial. Despite the abundance of work in this area, overall clinical outcome remains poor [10,70, 314]. Some studies report superior recovery following

immediate nerve suture whereas others advocate delayed suturing, and yet others report no marked differences [19,23,25,84,123]. The limited functional recovery of the facial nerve system following injury partly results from the failure of facial nerve axons to re-establish the correct connections [6,48] but also from hyperinnervation of their distal target muscle [5,279]. Functional regeneration occurs soon after nerve suturing, whereas changes in the somatotopy of the motoneurones within the facial nuclei are delayed: detectable in the cat at 4 months post-operatively [12], rather later than observed in rats (42 days) [5]. Age significantly affects the time course of recovery [312,313]. Following facial–facial anastomosis, i.e., suture of transected facial nerve, axonal regrowth is delayed for up to 4 weeks in the aged rats when compared to a young adult population [279]. Studies of adult cat spinal motoneurones have demonstrated only partial functional recovery of peripheral reinnervation, which is reflected in reduced dendritic sizes and inadequate branching patterns [30]. Central nuclear deafferentation due to glial intervention described above may play a very significant role in prevention of functional restitutio ad integrum but has not received sufficient attention on the clinical side. In patients with hypoglossal–facial anastomosis, there is evidence of central reorganisation of synapses [176,287].

## 8. Cell death in the facial nucleus

The extent of cell death in the central nucleus of origin of a peripheral nerve following injury is highly variable. In the adult rat, most facial motoneurones survive nerve transection [188,274]. This is in stark contrast to the response in adult mice where facial nerve axotomy causes up to half of the motoneuronal cell population to disappear [71,118]. Johnson and Duberley [127] estimate that between 17% and 25% of the motoneurones undergo cell death following facial nerve transection in adult Fischer 344 as well as Wistar rats, respectively. A greater incidence of neuronal death is reported following intracranial axotomy of the facial nerve close to the brain stem, i.e., close to the motoneuronal cell body in adult rats [187]. Neonatal axotomy induces massive motoneurone degeneration of facial [3,59,162,164,171,268] as well as spinal motoneurones [168,174,195,234,245]. In newborn rats transection of the facial and hypoglossal nerve results in the death of about 80% [310] and 60% [266] of axotomised motoneurones, respectively. Even less severe injuries like nerve crush result in the loss of a substantial number of the total motoneuronal population in the neonate. In an early light microscopic study by Soreide [268], only 10% of newborn rat motoneurones survived a crush lesion, compared to 100% following a similar lesion in adulthood. Several factors have been suggested to have a causal role in axotomy-induced degeneration of neonatal facial motoneurones. This includes the expression of high levels of excitatory amino acids and their analogues [36,100] and the generation of free radicals [107,235].

### 8.1. Molecular cell death pathways

As to the cell death mechanism involved following axotomy in rodents, this remains an area of intensive research. In the adult, apoptosis is completely absent from adult facial nuclei even if massive cell death is induced through avulsion or the application of neurotoxins. Some investigators have attributed the rapid demise of motoneurones to apoptosis as terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling (TUNEL) and in situ end labelling (ISEL) are positive [59,235,317]. However, there is irrefutable evidence now that these methods, which identify DNA fragments, are not specific for apoptosis [272]. For instance, in the axotomised facial nucleus TUNEL-stained microglia are seen [130]. Ultrastructural examination of these "TUNEL positive" microglia does not demonstrate any morphological features of nuclear apoptosis but TUNEL labelling was localised to the outer surface of the nuclear membrane and strong in the cytoplasm. This can be accounted for by DNA uptake from the few degenerating motoneurones post-axotomy [130]. We have discussed the specificity problem of TUNEL in a review on mechanisms of neuronal cell death [88], and a definition of aposklesis, the more likely form of cell death in the adult facial nucleus, has been provided [199]. In the latter recent study, we could show that following adult facial nerve axotomy, both peripheral nerve cut (Fig. 3) and crush injuries, trigger the de novo expression of α-synuclein in a small subpopulation of degenerating motoneurones in the adult rat facial nucleus. The level of expression of α-synuclein, a protein which normally occurs in presynaptic terminals [119,125], is related to the severity of neuronal injury, with a significantly larger number of labelled motoneurones de novo expressing α-synuclein following nerve cut than after crush injury [199]. A crucial role for α-synuclein in neuronal degeneration following peripheral nerve lesion is supported by the finding that abnormal accumulation of this protein is a feature of several neurodegenerative diseases including Alzheimer's and Parkinson's disease [14,271,308] and can be induced in nerve cells by neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [83,192,224].

In neonates, in contrast to the adult, classical apoptosis is seen. Several studies have investigated the time course of facial motoneurone degeneration following nerve lesion in neonatal rodents [37,59,235,310]. In neonatal mice operated soon after birth cell death is rapid [59]. All the motoneurones die by apoptosis within 120 h of nerve transection and removal of a distal segment, with a peak period 28 h post-injury [59]. In neonatal rats (P3), Casanovas et al. [36] observed a loss of more than 70% of the motoneurone population by 7 days after facial nerve

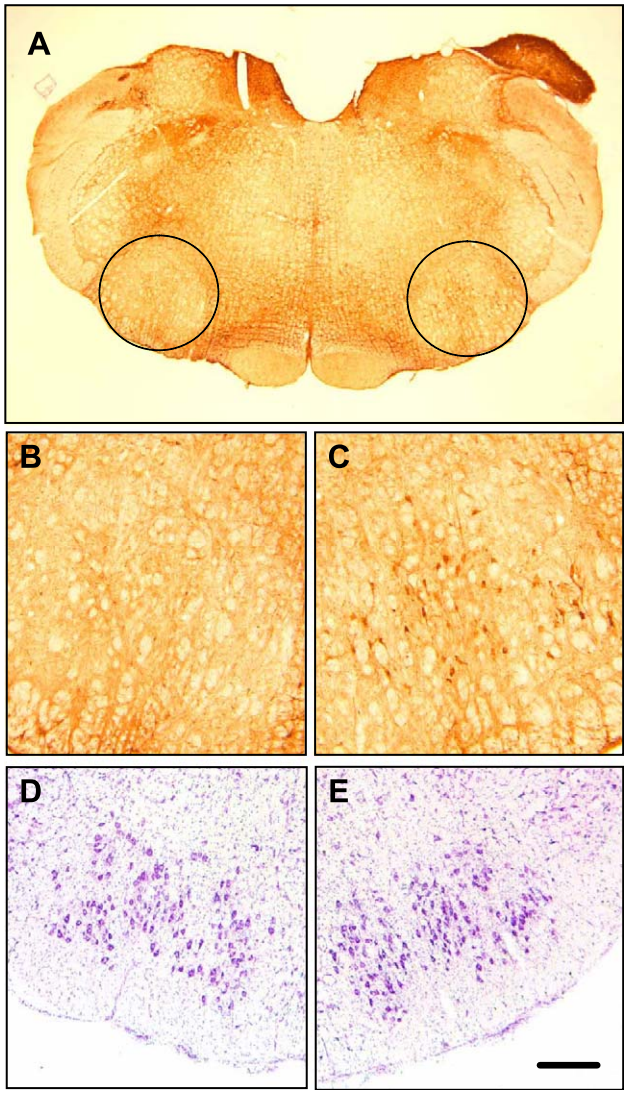


Fig. 3. Expression of α-synuclein in normal and axotomised motoneurones. (A) Cryostat section (10 μm) of the brain stem of an adult Wistar rat (9 days post-facial nerve transection) showing numerous α-synuclein immunoreactive motoneurones in the injured facial nucleus (right), whereas immunoreactivity is absent on the control side (left). These nuclei, control (B) and axotomised (C), are shown at higher magnification and in consecutive sections stained with Cresyl fast violet according to Nissl (D and E, respectively). Scale bar 200 μm.

transection. The cell death process continues slowly over several days, with a small number of degenerating neurones discernible throughout. A role for caspase-3, one of the 'effector' cysteine proteases, in axotomy induced facial motoneurone death has been proposed [311]. In the latter study, a three-fold greater survival of motoneurones in caspase-3 gene deleted mice when compared to age matched wild-type control mice was observed. This involvement of caspase-3 is not surprising as de Bilbao and Dubois-Dauphin [58] previously demonstrated that the application of peptide protease inhibitors, which preferentially inhibit caspase, reduce the number of TUNEL labelled motoneurones by 32% at 24 h post-injury. However, some motoneuronal death is observed in the absence of caspase-3 expression, which may suggest that the motoneurones 'decision to die' is made prior to or independent of the expression caspase-3 and may thus form a step in an alternative cell death pathway [311]. Bax, a proapoptotic member of the Bcl-2 family, has also been implicated in cell death following axotomy. Deckwerth et al. [61] in a study using a mouse knock-out model, neonatal Bax-deficient mice, report that following nerve transection, all facial motoneurones survive.

### 8.2. The developmental switch

Importantly, the developmental maturity of the animal at the time of facial nerve injury plays an important role and strongly influences regeneration outcome [268]. The same peripheral nerve lesion affects neonatal motoneurones much more severely than their adult counterparts. We therefore propose the existence of a 'developmental switch'. Nerve transection at birth results in almost complete cell death, whereas the same lesion at later stages of development results in very limited cell death in rats [162,171,212,268]. Similar age dependent neuronal vulnerability is seen in newborn rabbit motoneurones following facial nerve avulsion [301]. Olsson and Kristensson [212] observed a developmental change in the response of neonatal rat facial motoneurones to nerve transection, with the transition from rapid neuronal death during the early postnatal development to prolonged survival between P6 and P10. Similarly, Soreide [268] reported a rapid increase in the tolerance of rat facial motoneurones to axotomy from the first 2 postnatal weeks onwards. The vulnerability of neonatal motoneurones persists to the fourth week postnatally [133]. Two hypotheses have been advanced to account for this critical period ("developmental switch", vide infra) during early postnatal development. Firstly, motoneurones are critically dependent on their peripheral targets for trophic support [133,165]. This has been convincingly demonstrated in studies where a variety of neurotrophic factors were applied to the proximal end of a cut nerve (Table 1) or were reinnervation of the peripheral target musculature was shown to promote neuronal survival [133]. Secondly, the greater vulnerability may reflect the immature state of the cellular machinery involved in the response to injury [171]. This view is supported by the inability of immature motoneurones to mount a typical chromatolytic response [164]. Interestingly, a candidate molecule for the *developmental switch*, as we have come to refer to the phenomenon, has been presented recently (Fig. 4) [22]. Benn et al. [22] demonstrated that 12 h following sciatic nerve transection in adult rats, all injured sensory neurones and lumbar spinal motoneurones show induction and phosphorylation of the small heat shock protein 27 (Hsp27) (Fig. 4). However, the same injury in the neonate (P0) fails to induce Hsp27 expression in the majority of sensory neurones [166] and ventral horn motoneurones [22]. Degenerating motoneurones did not express Hsp27 and were positively stained for activated caspase-3

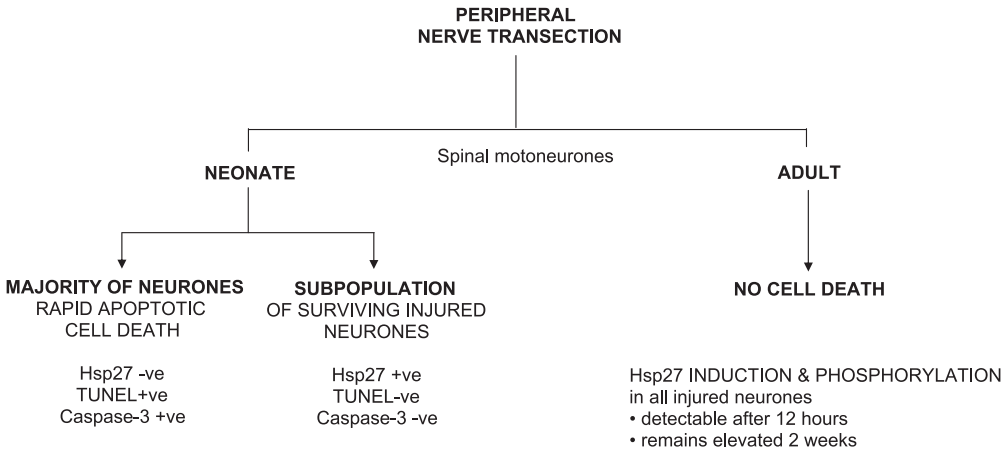


Fig. 4. Developmental switch. Hsp27 has been identified as a candidate molecule for the *developmental switch*. In the adult rat, all spinal motoneurones survive peripheral nerve axotomy and show the induction of Hsp27. In the neonate, however, nerve injury results in massive motoneuronal degeneration (unstained for Hsp27), with only a small population of motoneurones that survive. These surviving motoneurones express Hsp27, are negative for TUNEL labelling and do not express capase-3. This suggests a role of Hsp27 in neuronal survival [22]. Hsp27: small heat shock protein 27; TUNEL: terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling; + ve: positive.

and exhibited DNA strand breaks (detected by TUNEL) [22]. All surviving neonatal motoneurones expressed Hsp27. In fact, in vitro studies of neonatal sensory neurones show that Hsp27 protects neurones downstream of cytochrome *c* release from mitochondria and upstream of caspase-3 [22]. Many potential sites of actions have been proposed for Hsp27 [31,35,38,52,202,217,219] including the prevention of Daxx-mediated apoptosis by the interaction of Hsp27 with Daxx, a mediator of Fas-induced apoptosis [38]. In addition, Hsp27 promotes cell survival by preventing apoptosis via the regulation of cytochrome *c* release from mitochondria by interacting with Akt/PKB kinase [35,202], inhibiting Bid translocation to mitochondria [219], and by interfering with the mitochondrial pathway of caspase-dependent cell death [31]. Hsp27 may also directly inhibit the activation capase-3 [52,217]. This role for Hsp27 is in keeping with our own microarray data on the facial nerve system where Hsp27 is one of the genes seen to be up-regulated in adult facial nuclei 4 days after axotomy (unpublished data).

## 9. Future perspectives

The advent of new technological approaches such as microarray analysis [263] and laser capture microdissection [247] will allow a much more detailed analysis of whole brain regions at the cellular level. Microarrays make possible the systematic study of thousands of genes in parallel thereby providing a 'global molecular view' of the response to injury. We are currently using this technology to characterise the molecular programme of regeneration of the adult facial motoneurones following axotomy. The facial nucleus axotomy model will thus assume an important new role as a 'reference system' for microarray studies on tissues using human material that cannot be exactly staged and manipulated experimentally.

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