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# NEURONAL RECOVERY AFTER PERIPHERAL TRAUMATIC LESIONS OF THE FACIAL MOTOR NERVE

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**SUMMARY**

• *The present work summarizes recent data on the responses in the facial nucleus to experimental lesion on the extratemp oral part of the facial nerve. It includes a description of all so far reported reactions to axotomy in motoneurons, microglia and astroglia at cellular and molecular level, together with an attempt for a comprehensible interpretation of their importance. The brief review on the experimental and clinical results of the reinnervation is followed by some original results from our experience to improve neuronal regeneration with peroral administration of the calcium antagonist nimodipin.*

**INTRODUCTION**

• The facial nerve is the most emotive nerve in the human body. Its motor (mimic) function accounts for one's facial tone, voluntary facial movement, and involuntary emotional expression of the face, i.e. the aesthetic appearance of an individual, which is so important for social life. That is why the dysfunction of the facial nerve in combination with the grotesque disfigurement may often lead to a psychological incapacitation (1-3).

Unfortunately, the facial nerve is the most frequently affected cranial nerve in head and neck trauma. The lesion of the facial nerve are usually postoperative (removal of cerebellopontine angle tumors, acoustic neuroma surgery, parotid resections for malignancy) or consequences of traffic accidents (brainstem hemorrhage, temporal bone fractures, or lacerations of the face).

To date all modern surgical approaches for treatment of the facial palsy are aimed at creating favourable conditions for accelerated centrifugal regrowth of the facial axons towards their peripheral targets. These include the immediate end-to-end suture of the transected facial nerve (facial-facial anastomosis), suture of the proximal stump of a transected hypoglossal nerve to the distal stump of the facial nerve (hypoglossal-facial anastomosis) and microsurgical implanting of grafts harvested from the sural (2) and/or radial (3) nerve.

Synchronously with the advancing sophisticated neurological techniques and high-tech tools, much attention was given to improve the process of regeneration of the facial motoneurons in the brainstem. Before reaching this goal, however, voluminous experimental work was performed on the reactions in the facial nucleus after injury of the peripheral nerve. The results obtained attempted to answer several major questions: (i) what are the morphological changes that occur in the facial nucleus after transection of the facial nerve, (ii) is there a correlation between the severity of the lesion and the final

neurological outcome, (iii) is the subsequent function as good as normal, and (iv) can the process of regeneration be accelerated?

The aim of the present paper is to provide an overview and interpretation of the answers to these questions, i.e. this review deals with the neuronal and glial changes in the facial nucleus in response to the most common experimental injuries on the extratemporal portion of the facial nerve in adult rats. It includes neither a description of the post-lesion changes along the peripheral nerve fibers themselves, nor any data about the post-traumatic reinnervation of the motor end-plates of the mimetic musculature. Hence, this script is concerned only with the events in the motoneurons and surrounding neuroglia after the peripheral (axonal) lesion of the VII cranial nerve.

## CHANGES IN THE FACIAL NUCLEUS AFTER TRANSECTIORI OF THE FACIAL NERVE

### • Neuronal and glial changes at the cellular level

• *Neuronal changes*

The first systematic review on the consecutive changes in the facial motoneurons induced by avulsion of the facial nerve in rabbits has been presented by Franz Nissl on 9th November 1890 (4). He demonstrated a disintegration of the "chromatin" bodies in the lesioned pertkarya beginning within the first 24 h after the lesion. Later, it became clear that the classical term "chromatolysis" involves the dispersion and hypertrophy of the neuronal rough endoplasmic reticulum (5). However, a recent quantitative analysis of chromatolysis revealed that this reaction starts within 8 h after axon transection (6).

Within 3 days after axon injury, the facial motoneurons increase in profile area (7). The increase of neuronal soma, nuclei, and nucleoli has been measured morphometrically to reach 30-40% between 10 and 21 days post axotomy (8) and has been interpreted as a correlate of the accelerated synthesis of rRNA (9) or as a reflection of the transient transcription of mRNA (8).

*Glial changes*

The microglial cells proliferate and reach a perineuronal position, thus isolating the neurons form their synaptic inputs (10-13). This displacement of boutons by microglial cells is probably preceded by a loosening of the synaptic contacts, due to some changes in the membranes of the lesioned motoneurons (10).

### Neuronal and glial changes at the molecular level

*Neuronal changes*

The ***direct self-defence mechanisms*** of the lesioned neurons are immediately activated. One of them is the recently shown expression of nitric oxide synthase (NOS) in axotomized facial motoneurons, which is considered to counteract the massive increase in free radicals consequent to axonal injury and thus supports the anabolic programme for regeneration of the damaged axons (14).

Another molecular mechanism for direct neuronal self-protection may be the migration of the cytosolic enzyme neuron-specific enolase (NSE) into the nuclei of the axotomized neurons (15). The neuronotrophic effect of the intranuclear NSE may be attributed to the resulting pyruvate which has a potent neuronal survival-promoting action by protection of the whole intracellular machinery against peroxide-induced damage (16). A strong support to this hypothesis is the statement that NSE directly promotes the survival of embryonic rat neurons in primary culture (17).

A third molecular protection is the dramatical increase in content of the possibly neurotrophic factor calcitonin gene-related peptide (CGRP) following transection of the facial nerve (18-21). It is known that CGRP stimulates the activity of adenylate cyclase leading to an accumulation of cAMP, thereby regulating acetylcholine receptor synthesis (22,23). On the other hand, CGRP has been suggested a putative diffusible signalling factor for the activation of the surrounding glia (21). This notion is partially confirmed by the established dependence

of glial fibrillary acidic protein (GFAP) mRNA synthesis on high cAMP levels (24). Further, it is suggested that (i) due to the rapid accumulation of interleukin (IL)-6 mRNA in the facial nucleus, IL-6 might also act as an early acti-vating signal for glial cells after axotomy of the facial nerve, and (ii) the triple increase of transforming growth factor (TGF)-pl mRNA in the activated microglial cells around regenerating motoneurons provides a long-lasting negative feedback signal controlling glial activation (25).

Also at the mRNA level it has been shown that a particular family of genes might play a crucial role in adaptive plasticity and in long-term changes in the nervous system. These are the immediate early genes (IEG) which transcription is activated rapidly within minutes after axotomy. Damage to the facial axons causes a unique increase in the mRNAs of c-jun and jun B in the facial nucleus (26-29). The clear temporal and spatial correlation between c-jun/jun B mRNA expression and the induction of the CGRP gene in the injured facial nucleus shows that the CGRP gene could be one of the targets of c-jun and jun B (26).

The neuronal survival programme of the axotomized neurons disposes with a wide spectrum of ***indirect*** *self-defence* ***mechanisms,*** i.e. reactions which are not directly aimed against neuronal death. One of them is the switch from a mode of homeostatic cell maintenance to a mode of intense biosynthetic activity, including both increase of RNA content and uptake of amino acids in motoneurons (5). The activity of ornithine decarboxylase, akey enzyme in the polyamine biosynthesis (responsible for the production of neuronal growth factors), reaches 300% over control (30). The activity of trans-glutaminase, the putable enzyme through which the polyamines exert their effects, alsoincreases (31). Thetransection of the facial nerve is followed by an increased intraneuronal uptake of glucose (32) and iron, the latter being accompanied by an enhanced immunoreactivity of transferrin receptors (33). The increased consummation of glucose is directed to the pentose phosphate shunt which is also activated after axotomy (7,34,35), The pentose phosphate shunt is known to be involved in the production of ribose and NADPH. Ribose is necessary for the increased synthesis of RNA, and NADPH furnishes proton equivalents for the synthesis of lipids necessary for membrane restoration during axonal regrowth and sprouting (7). In frame of this intensive regeneration programme, the synthesis of cytoskeletal proteins, tubulin and actin, is also increased (36-38) and newly synthesized "growth associated proteins" (GAP) appear (39).

In addition, studies have also shown that some proteins generated during the axon reaction are not normally found in the perikaryal cytoplasm of adult neurons (40). The developmentally regulated tubulin mRNA and also GAP-43 mRNA have been found to be rapidly induced in regenerating adult facial nuclei (37,41).

There occurs a decrease in the synthesis of transmitter-related compounds, i.e. enzymes or receptor proteins. The activities of some enzymes involved in transmitter metabolism such, as dopaminehydroxylase, tyrosinehydroxylase, choline-acetyltransferase, and acetylcholinesterase (asymmetric and globular forms) decrease in response to axotomy (42-46). The general neuronal activity, as judged upon by the established decrease in activity of cytochrome oxidase (45), is also diminished. In addition, the synthesis of the 68 kD and 150 kD neurofilament proteins is decreased (36).

*Glial changes*

The retrograde changes at the molecular level after axotomy are not limited only to the neurons, but also involve the surrounding microenvironment of glial cells. By supporting neuronal growth and metabolism glial cells may determine, in part, the degree of recovery after injury. Whereas in has been shown that astroglia actually supports neuronal growth and survival (47-49), cell culture studies indicate that microglia can release cytotoxic agents (50-52). The ramified quiescent microglia comprise a regularly spaced network of cells within the facial nucleus of the rat. In response to sublethal injury of the facial motoneurons (eg. transection of the facial nerve) these resting microgliocytes show a dramatic increase in mitotic activity and rapidly migrate toward

the neurons (12,53,54). Upon reaching the neuronal cell surface, the microglial cells displace the afferent synaptic terminals (10) and increase the synthesis of cell adhesion molecules (55) which enable them to bind into uninterrupted rings around the lesioned neurons.

The presence of activated microglial cells around lesioned neurons (regardless of the type of injury), however, does not always result in neuronal death (56,57). Light microscopical and ultrastructural histochemistry revealed high activity of the ectoenzyme S'-nucleotidase on the membranes of the microglia (58-60). Recently, this finding was further precized by showing that 5'-nucleotidase immunoreactivity is predominantly associated with perineuronal microglia (61) which have been implicated in the lesion-induced detachment and displacement, or "stripping" of synapses from the lesioned motoneurons (10,13,53,61). This enzyme produces some nucleotides and adenosine which are potent regulators of vascular tone, and also affect neural and immune cellular activities (62-66).

A challenging issue for understanding any degenerative CNS disease, especially immune-mediated injury, is whether brain-associated immune cells are capable of doing both phagocytosis and antigen presentation (13,67-79), and their interactions with T-lymphocytes passing through the blood-brain barrier (80-82).

The astroglia response to axon reaction is initially confined to a slight hypertrophy which is difficult to quantify and specify (83). It is the paper of Graeber and Kreutzberg (84) that marks the beginning of a reliable assessment of the participation of astrocytes in the axon reaction, i.e. the immunohistochemical demonstration of GFAP-positive staining in the reactive astrocytes. GFAP is the cell-specific intermediate filament protein in astro-cytes and the upregulation of its synthesis is considered a definite feature of activated astroglia. Employing this reliable method, Greaber and Kreutzberg (85) show that three weeks post axotomy the reactive astrocytes start to form thin lamellar processes which separate the neuronal perikarya and adjacent presynaptic boutons for several months. This gross alignment of postsynaptic membrane and presynaptic boutons is considered a prerequisite for functional recovery (57). The upregulation of GFAP content in the astrocytes starts 12 h after nerve lesioning and the time course and extent of the GFAP synthesis are strongly influenced by successful or unsuccessful regeneration (86). Recent data, however, provide evidence that the increased synthesis of GFAP is preceded by an enhanced coupling capacity of astrocytes: as early as 45-90 min after transection of the facial nerve in rats, there occurs an increase in the immunoreactivity of the predominant gap junction protein in astrocytes connexin 43 (87).

## CORRELATION BETWEEN THE SEVERITY OF THE LESION AMD THE FINAL NEUROLOGICAL OUTCOME

H Depending on the outcome there are two major groups of experimental injuries. Those from the first group provide conditions that favour neuronal regeneration. Alternatively, the experimental lesion included in the second group impede the axonal resprouting and thus provide models for studying neuronal degeneration and neuronal death.

Following nerve lesions from the ***first group*** all facial motoneurons resprout branching axons which succeed to reach peripheral targets. Due to the reestablished nerve-muscle contract the motoneuronal perikarya in the brainstem of adult rats are able to survive the insult from the injury, i.e. they successfully regenerate. This "regeneration group" includes the following experimental injuries: crush (8,45,88,89), transection (14,44,46,54,83,87-90), sequential double transection known also as conditioning lesion (7), transection and immediate end-to-end suture (6,56,92,93), transection and immediate suture to the hypoglossal nerve, i.e. hypoglossal-facial anastomosis (HFA)(15,57,94), the latter deserving a special attention.

First, HFA is a standard method for the surgical treatment of facial palsy in man: the end-to-end suture of the freshly transected normal hypoglossal nerve to the distal stump of the transected facial nerve enables the outgrowth of hypoglossal axons into the paralyzed facial plexus. As a result, the

mimetic musculature of the human face is reinnervated up to aspontaneous, i.e. subconscious smiling, which indicates a remarkable degree of neuronal plasticity in the brainstem or higher motoric centers of man (95-101). Our own experiments show that despite the resprouting of hypoglossal axonal branches into the mimetic musculature, axons of the transected facial nerve (left untreated during operation) also resprout and reach the facial muscles. Eight weeks after HFA there are 43% more motoneurons (hypoglossal and facial together) that project to the rat whiskerpad muscles than in normal animals. This "hyperinnervation", i.e. the projection of more motoneurons into the target muscle than under normal conditions, is persistent and constant up to 32 weeks post operation (94).

A comparison of the time course of this dual resprouting shows that between 14 and 28 days post operation (dpo) the facial muscles are reached and consequently innervated by hypoglossal motoneurons. This may result in normalization of both trophic secretion and expression of neural cell adhesion molecules (N-CAM) (102) and thus it should prevent any later ingrowth of axons. Furthermore, between 42 and 56 dpo, the total amount of nerve fibers that supply the whiskerpad (facial and hypoglossal together) equals that under normal conditions. Despite of this, both hypoglossal and facial motoneurons continue to send axons to their new or original area of innervation, causing the hyperinnervation. What are the regulatory mechanisms of this development? Some biophysical properties of the normal hypoglossal motoneurons of the rat (103) are almost identical with those of the normal facial neurons of the rat (104,105). This is, however, not the case as the active biophysical characteristics of the hypoglossal and facial motoneurons are concerned. The frequency of discharge of the hypoglossal motoneurons is 5.2±0.6 per minute (106,107), i.e. about O.lHz. This frequency of impulses, however, is far lower than that of the original facial supply of the whiskerpad. During exploration the rats move their mystacial vibrissae back and forth at a rate of about 7 Hz and additionally display a tremorlike movement of the vibrissae at 9 Hz (108). Therefore, the muscles of the whiskepad are not adequately stimulated by the hypoglossal motor activity and hence continue the secretion of reinnervation-promoting factor(s) (109).

These new results from the HFA paradigm confirm the major role and highest demands of peripheral targets in the process of reinnervation. Evidently, under this experimental protocol, it seems rather easy to achieve conditions for axonal resprouting and neuronal regeneration in rats. Practically all neurons survive after facial-facial anastomosis (56). Unfortunately, in a vast portion of patients the facial palsy is due to postoperative removal of cerebellopontine angle tumors or acoustic neuroma surgery (2,110) after which there are no regenerating neurons left in the brainstem. Thereanimation of the facial musculature in rats obviously requires the employment of such experimental approaches which prevent the spontaneous axonal regrowth and thus induce neuronal degeneration.

These approaches are the object of *thesecond* ***group*** of nerve lesion after which there occurs no resprouting of the facial motoneurons and a large portion of neurons gradually die. The lesions included in this "degeneration group" are: transection and avulsion by gentle traction (88,89), injection of toxic ricin (75,78,111), resection, i.e. transection and removal of 10 mm nerve length (37,56,57,86,94, 112-115).

The most intriguing reaction in the facial nucleus after all severe lesions to the facial motoneurons concerns the microglia. Following any lethal injury of motoneurons the activated microglia do not only express all reviewed immune-related changes (see above), but develop into full-blown macrophages (111). These phagocytic microglia, however, do not only remove the debris of the dead motoneurons, but can present antigens to T-lymphocytes and initiate an immune response (11,78,82). Long-term studies from our laboratory employing retrogradte labelling of the facial metoneurons with Fluoro-Gold prior to resection of the facial nerve show that following completion of phagocytic activity, the neuronophages migrate toward adj acent degenerating cells from the same lesioned neuronal pool (112,113,116,117).

**IS THE SUBSEQUENT RESERVATION AS GOOD AS NORMAL?**

3 Functional recovery after lesions of the facial nerve is usually poor, the major reason for this being the misguidance of the regenerating fibers to inappropriate peripheral targets (92-94,118). Despite the use of presently available microsurgical techniques for repair of injured peripheral nerves, i.e. clean wound, gentle tissue handling, good adaptation and coaptation, minimal number of sutures, and absence of tension (119), there always occurs a substantial mismatching of motoneurons and muscles following transection and subsequent regeneration within a nerve trunk.

After nerve transection in adult animals virtually all neurons survive, but the regenerating axons seem to grow in a relatively random manner resulting in a considerable disarray of the facial nucleus. This loss of somatotopic organization in the facial nucleus following injury of the peripheral nerve is the morphological correlate of the phenomenon of misdirected resprouting termed also excessive reinnervation, aberrant reinnervation, aberrant regeneration, or misdirected regrowth of axons. As a consequence, the coordinated activity of individual muscles is impaired (120-122) and abnormal associated movements (synkinesis), hemifacial spasms, or contractures may develop (123).

**IMPROVEMENT OF MEUROMAL REGEMERATIOH**

• In an attempt to improve axonal resprouting we performed a pharmacological experiment that was aimed at testing a favourable effect of the calcium channel blocker nimodipine on neuronal plasticity (124-126). Following HFA, nimodipine treatment, and injection of horseradish peroxidase (HRP) into the mimetic musculature of rats, we counted the retrogradely labelled motoneurons in the brainstem at various postoperative survival times. The comparison of these neuron numbers with data from experimental animals notsubjected to nimodipine treatment (placebo), showed that the peroral administration of the drug has two beneficial effects (127). First, it shortens the time for the successful sprouting of the axotomized hypoglossal axons into the facial periphery by 50%. Our quantitative estimates show that in nimodipine-treated animals the sectioned hypoglossal axons reach the whiskerpad muscles 14 days earlier than in placebo-fed rats (first HRP-labelled neurons at 28 dpo). In this way, the proposed favourable effect of nimodipine on neuronal recovery (128,129) is expressed by a significant acceleration of the axonal resprouting. We cannot provide evidence about the morphological and molecular events that accompanied this increased rate of recovery since the precise mechanism of action of the drug is still unknown (130 for review). Anyway, a dual effect on both perikarya and neurites may occur. First, direct neuronotrophic effect has been already suggested: as nimodipine passes the blood-brain barrier and binds to specific dihydropyridine receptors, it possibly prevents the influx of $Ca^{2+}$ into the injured neuronal cell bodies (91,131-135). Second, peripheral beneficial effect of nimodipine on the axonal branches may also involve the fine regulation of intracellular calcium in outgrowing sprouts (136).

These two possible effects of the drug are added to a third factor, i.e. the enhanced hypoglossal sprouting due to the crossed nerve suture: the significant difference in fiber numbers between the facial and the hypoglossal nerve creates a situation in which the hypoglossal axons are guided by 40% more rows of Schwann cells during their regrowth (57,94). In our opinion, it is not the single action, but the combination of all three neuronoprotective effects that ensures this improved recovery (126,137).

The second favourable effect of the administration of nimodipine in rats with HFA is that it completely prevents the pathological hyperinnervation and causes a statistically significant suppression of the spontaneous misdirected resprouting of the facial motoneurons. Like in the placebo-fed animals after HFA, a misdirected resprouting of the facial axons occurs (first detected 6 weeks after HFA), but the number of resprouted facial motoneurons remains 38% less than in placebo-fed animals.

Apart from the fact that this lower neuron number does not lead to a hyperinnervation, there seems to occur a strange effect of the drug: on one side, it has

a stimulatory influence on the sutured stump of the transected hypoglossal nerve, and on the other, a suppressive effect on the proximal stump of the transected facial nerve.

Based on two major considerations (i) it is very unlikely that nimodipine may have had a selective action on these two types of brainstem motoneurons, and (ii) the suppression of the facial resprouting starts from its very beginning, we suggest that this strongly limited sprouting of the facial axons is not due to a suppressive effect of nimodipine, but rather to the very rapidly occurred hypoglossal reinnervation of the whiskerpad. In placebo-fed animals, the first axons of the facial motoneurons reach whiskerpad muscles between 28 and 42 dpo in a period when already about 570 hypoglossal motoneurons project there. This retardation (within the next 2 weeks) and the ratio between hypoglossal and facial neurons of 2:1 provide evidently good grounds for a competitive relationship which yields in a prolonged hyperinnervation of the whiskerpad (94). Under nimodipine treatment, however, the situation is very different. Due to accelerated resprouting (see above), the hypoglossal axons reach the facial periphery very early and are the only neurites in the target area for a twice as long period (from the 2nd till the 6th postoperative week) than in placebo-fed animals.

Till 7 dpo, no motor axons supply the mimetic musculature and the denervated facial muscles intensively secrete molecules that promote neuronal survival (109) and accumulate N-CAM that enhance their attractiveness to axons (102). Between 7 and 14 dpo the facial muscles are reached and innervated by the hypoglossal motoneurons. This reinnervation is, however, completely different from the one that occurs in the placebo-fed animals.

During reinnervation following nerve crush, there is a period when the motoneurons reach neuromuscular junctions, but do not release neurotransmitters (138,139). The first miniature end-plate potentials (MEPP) reappear approximately 2 weeks after the crush-lesion (140). Especially in these early stages of reinnervation, however, the $Ca^{2+}$-dependent release mechanisms are highly efficient, i.e. the influx of $Ca^{2+}$ increases the frequency of MEPP. The reason for this is "the low buffering capacity for free intracellular $Ca^{2+}$ of the regenerating nerve terminals, which would allow a stronger stimulatory action of the $Ca^{2+}$ which has entered the presynaptic ending". In spite of this very high efficiency, however, the MEPP frequency remains far below normal (141).

The nimodipine treatment reduces the calcium influx into the axoplasm of the resprouting nerve fiber (136) and further reduces its buffering capacity for $Ca^{2+}$. This might render the responsiveness of the terminals to $Ca^{2+}$ even stronger which would yield MEPP with even higher frequency. In this way, a much earlier and qualitatively better reinnervation of the facial muscles is achieved, that leads to a partial normalization both of trophic secretion and N-CAM expression. This results in a significant decrease of the misdirected re-sprouting of facial nerve fibers, there occurs no-competitive relationship between the facial and hypoglossal motoneurons, and no hyperinnervation.

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