Muscular reinnervation and differentiation after peripheral nerve transection
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INTRODUCTION
A considerable percentage of major injuries affecting the extremities e.g. due to sports and traffic accidents are complicated by a peripheral nerve lesion. Upper extremities are affected in most cases and if so, the ulnar nerve is involved in 30%. In the lower extremities often the peroneal nerve is lesioned (50%) or the lumbosacral plexus (25%)40. In human babies peripheral nerves may be disrupted as a consequence of complicated birth51, the mean incidence of these lesions being 0.12% of all births28.

The most serious complication is a total disruption of the nerve (neurotmesis), and this requires surgical realignment. Often the nerve is damaged over a certain distance and moreover, the disrupted nerve stumps tend to retract. Suturing both stumps is only possible in case of a sharp transection and without mechanical tension at the coaptation site. However, when the gap between the proximal and distal nerve stumps is too large, a device is needed to bridge this gap in order to guide the outgrowing nerve fibers and to prevent the formation of a neuroma. Autologous nerve grafts are most widely used in such situations and often a sensory nerve is transplanted, such as the sural nerve. In recent years, knowledge of the factors influencing the quality of a nerve reconstruction has increased and a variety of materials have been tested in artificial nerve guides (for review see32).

Progress in surgical techniques and the application of recently developed nerve guides have considerably improved the prospects for reinnervation of the deprived target areas. Despite successful reinnervation, however, functional outcome often is disappointing35;36;38. One of the reasons for that is an at random reinnervation of the target areas by the newly outgrowing nerve fibers (e.g.,18). A field of research that has been relatively neglected is the effects of a nerve transection and a temporary denervation on muscle morphology and the at random reinnervation of the muscles. This field is the topic of the present thesis, the objective being that insight into these neuromuscular factors might further elucidate our understanding of the disappointing clinical outcome after a nerve repair and it possibly might give directions for improved therapeutical strategies.

Most of the experimental research on peripheral nerve trauma has been performed in the rat1;4;7;8;16;18;19;25-27;31;33-35;37;47;48. Regeneration after transection has also been studied e.g. in crayfish43, tench6, frog20;42, guinea pig9, mouse50;52, rabbit13 and cat17;45. The nerves, which have been studied mostly are the sciatic nerve19;21;25-27;33-35;37;53, the facial nerve (for review see19) or the nerve to the gastrocnemius muscle14;15, and also e.g., the optic nerve6 the trigeminal nerve22 and terminal branches of the brachial plexus1. In this thesis the effects will be investigated of a transection of the sciatic nerve in adult and in young rats.

The sciatic nerve in the rat originates in the sacral plexus and bifurcates into two main branches, the tibial and common peroneal nerve. These nerves innervate several hindleg muscles, involved in flexion and extension of the knee and ankle joint as well as the skin of the lateral side of the calf and the fifth digit.
As also in clinical situations often mixed nerves (containing motor, sensory and autonomic fibers) are affected, the sciatic nerve is an excellent model to study the complexity of reinnervation by evaluating the motor and sensory recovery\textsuperscript{24}.

When the sciatic nerve is transected in adult rats, both motoneuronal and sensory axons are severed and, if the transection is not too close to the soma, and in case of a reestablishment with the target areas, the neurons generally survive. The motor and sensory axons sprout and, when adequately guided they tend to grow along the remains of the distal part of the nerve\textsuperscript{3;19;21;25-27;33-35;37;53}. A major problem is, however, that the outgrowing nerve fibers randomly reinnervate the denervated muscles (and also, skin areas). Bodine-Fowler and coworkers\textsuperscript{3} injected two retrogradely transported fluorescent dyes in the soleus muscle of young adult rats, one before transection and the other after reinnervation of the muscle. Only around 16% of the motoneurones were labeled by both dyes, indicating that only these had reinnervated their genuine target muscle. Remarkably, however, the total number of motoneurones labeled from the reinnervated soleus muscle had increased to around 2.5 times that figure before transection\textsuperscript{3}. Similar results were obtained by Streppel and coworkers\textsuperscript{48}. They injected retrogradely transported horse radish peroxidase (HRP) in the whisker pads of young adult rats after transection of the facial nerve and they observed an increase by 30% in the number of motoneurones labeled from the facial muscles in the pad-area after reinnervation\textsuperscript{48}. They also found an increase in the territory of the "pool" of motoneurones innervating these muscles. In adult rats, we studied the motoneuronal pools of the gastrocnemius, the soleus and the tibialis anterior muscles after sciatic nerve transection. Retrogradely transported unconjugated Choleratoxin subunit B (CTB) was injected into the muscles and we also observed an increase in the territory of the motoneuronal pools at the operated side but no considerable deviations in the numbers of motoneurones at the affected side\textsuperscript{18}. Both the findings of Bodine-Fowler and our own results indicate an at random reinnervation of muscular targets by the outgrowing axons. Recordings of EMG patterns during walking in these rats further substantiated these findings. In normal rats during walking, a tonic burst in the gastrocnemius muscle accompanied the stance phase whereas the swing phase was preceded by a shortlasting and brisk burst in the tibial muscle, the limb flexor. After reinnervation, however, the bursts in the gastrocnemius muscle became markedly irregular and we often observed a coactivation of the tibial and the gastrocnemius muscles, both during the stance phase and the swing phase. In summary, after transection of the sciatic nerve at a proximal level, innervating by its branches a variety of antagonistic muscles, each of the muscles is reinnervated by both genuine and foreign motoneurons, and this leads to abnormal EMG patterns.

Important factors which might contribute to functional impairments is the effect of a denervation and subsequently an abnormal reinnervation (as in the
cases described above) on the properties of the muscles. It is known that certain properties of muscle fibers change after reinnervation and also after changes in activation patterns\textsuperscript{3;5;12;44}. Buller and coworkers studied the effects of a “cross innervation” on muscle properties\textsuperscript{5}. In these experiments in cats, a nerve innervating the slow soleus muscle was implanted into the fast flexor digitorum longus muscle and vice versa. The fast muscle became slow and the slow muscle became fast as indicated by measurements of the contraction time. Buller concluded that after reinnervation, the properties of the muscle fibers adjust to the characteristics of the motoneurones. This hypothesis was supported by several investigations in the following years in which changes in the muscle fibers were observed both with physiological as well as histological techniques\textsuperscript{10;11;46}.

As functional impairments frequently are observed after peripheral nerve injuries at adult and also at young age\textsuperscript{29}, we decided to study the effects of a nerve transection on muscular properties such as fiber type composition and (re)innervation patterns of the muscles. Results might further elucidate the factors which are responsible for functional impairment after a nerve transection with aberrant reinnervation patterns and they possibly might point to possibilities for treatment.

We transected the sciatic nerve in adult rats and studied the effects on the muscle fiber distribution of the gastrocnemius, soleus and tibial muscles (chapter 2) as well as on the innervation patterns of these muscles (chapter 3) until 21 weeks after the transection. The problem whether fiber type distributions and innervation patterns remain unaltered even after long survival periods was studied in the soleus muscle, 60 weeks after a sciatic nerve transection (chapter 4).

It is suggested from clinical experience that damage to peripheral nerves in babies or children has less serious functional effects compared to adults\textsuperscript{2;23;30;41;49}. We studied whether this notion holds in controlled animal experiments and the specific question is whether sciatic nerve transections at young age have other, and possibly less serious consequences than at adult age. It is well known from other research that nerve transections at neonatal age lead to massive motoneuronal cell death. The first problem of this second part therefore aimed at identifying the youngest age at which still appreciable numbers of motoneurones survive. To this, we studied the effects of a sciatic nerve transection at ages from the 4\textsuperscript{th} day after birth until the 40\textsuperscript{th} day (chapter 5). On the basis of the results of this study we transected the sciatic nerve at the 10\textsuperscript{th} postnatal day and studied the rat’s motor performance (chapter 6), and EMG patterns during locomotion as well as the morphology of the motoneuronal pools labeled by CTB (chapter 7). The morphology of the reinnervated soleus muscle after transection of the sciatic nerve at P10 was studied at 60 weeks (chapter 8). In the final chapter (chapter 9) the results of this thesis and recommendations for future research are discussed.
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