

List of Contents

1	Outline of the General Neurobiological Problem	1
1.1	The Perikarya Supporting Axonal Regrowth Are Hyperexcitable	1
1.1.1	Increase in Biosynthetic Activity	1
1.1.2	Hyperexcitability of the Axotomized Perikarya	2
1.2	Axonal Regrowth Is Compromised by Ephaptic Cross-Talk Between the Branches	3
1.2.1	The Endoneural Micro-Environment Permits a Rapid and Extensive Axonal Growth	3
1.2.2	Excessive Firing by the Transected Axons	3
1.3	Biological Significance of Axonal Branching	3
1.4	Role of the Cytoskeleton Reorganization During Axonal Regrowth	5
1.4.1	The Role of Cytoskeletal Proteins in Axonal Elongation	5
1.4.2	Role of Cytoskeletal Proteins in Axonal Branching at the Growth Cone	8
1.4.3	Role of Cytoskeletal Proteins in Collateral Axonal Branching at the Axon Shaft	8
1.5	The Individual Guidance Cues Promoting Reinnervation of Original Targets Are Still Unknown	9
1.5.1	ECM Glycoproteins, Axonal Regrowth, and Pathfinding	9
1.5.2	Increased Production of Trophic Factors	10
1.6	Conclusion	12
1.7	Outline of the Clinical Problem	13
1.8	Question Still Open	14
1.9	Methodological Approach	14
2	Materials and Methods: Experimental Sets	14
2.1	First Set of Experiments: Attempts to Reduce Collateral Axonal Branching by Alterations of the Trigeminal Input to the Facial Perikarya	15
2.1.1	Effect of Altered Trigeminal Input to Facial Perikarya on Axonal Branching as Estimated by Application of Crystalline Tracers to Transected Superior and Inferior Buccolabial Nerves	16
2.1.2	Effect of Altered Trigeminal Input on the Rate of Axonal Elongation	20
2.1.3	Effect of Altered Trigeminal Input to Axotomized Facial Perikarya on the Accuracy of Reinnervation	21
2.1.4	Effect of Altered Trigeminal Input to Axotomized Facial Perikarya on the Compound Muscle Action Potential (CMAP) of the Vibrissal Muscles	22
2.1.5	Effect of Altered Trigeminal Input on the Recovery of Vibrissae Motor Performance Estimated by Video-Based Motion Analysis	24

References	109
Subject Index	131

3.2.3.1	Unoperated Rats	71
3.2.3.2	General Features of the Facial Nucleus After Transection of the Facial Nerve	71
3.2.3.3	Varying Effects of the Neutralizing Antibodies on the Increased Number of Axons and Neurons in the Three Main Branches (Rami) of the Regenerating Facial Nerve	79
3.2.3.4	Effects of Neutralizing Antibodies on Axonal Branching as Estimated by the Portions of Double- and Single-Labeled Motoneuronal Perikarya	80
3.2.4	Transplantation of Olfactory Ensheathing Cells, Schwann Cells, and Bone Marrow Stromal Cells Does Not Alter Axonal Branching of Regenerating Facial Motoneurons	82
3.2.4.1	Determination of the Degree of Axonal Branching	82
3.2.4.2	Biometric Analysis of Whisking Behavior	82
3.2.5	Transplantation of Autologous Olfactory Mucosa Does Not Increase the Accuracy of Reinnervation but Promotes Functional Recovery of Vibrissal Motor Performance	82
3.2.5.1	Transplantation of Olfactory Mucosa Reduces the Collateral Axonal Branching	82
3.2.5.2	Transplantation of Olfactory Mucosa Does Not Increase the Accuracy of Reinnervation	86
3.2.5.3	Transplantation of Olfactory Mucosa Promotes Functional Recovery of Vibrissal Motor Performance	88
4	Discussion	91
4.1	The Combined Approach to Evaluate the Quality of Peripheral Nerve Regeneration	91
4.2	Sensory-Motor Integrity as a Factor in Motor Regeneration	92
4.2.1	Rationale for Using the Combined Trigemino-Facial Lesion Model to Study Neuronal Regeneration	93
4.2.2	Axonal Branching as a Component of Misdirected Target Reinnervation	94
4.2.3	Lesion of the Contralateral Trigeminal Nerve Attenuates the Branching of Transected Facial Axons and Improves the Accuracy of Target Reinnervation	94
4.2.4	Nature of the Beneficial Effect of the Accompanying Lesion	95
4.2.5	Clinical Implications	97
4.2.6	Recovery of Whisker Movement in Blind Rats Is Probably Due to an Extraordinary Plasticity of the Facial Motoneurons Induced by Putative Behavioral Demand and Early Forced Overutilization	98
4.3	Manipulations of the Conditions at the Lesion Site Cause Changes in the Quality of Axonal Regeneration and Recovery of Function	98
4.3.1	The Use of Extracellular Matrix Proteins to Improve Reinnervation	98
4.3.2	Role(s) of Trophic Factors in Axonal Regrowth and Effect of Their Neutralization	101
4.3.3	The Use of Cell Transplantation for Improving Reinnervation	104
4.3.4	The Beneficial Effect of Transplanted Olfactory Mucosa May Involve a Moderate but Long-Lasting Secretion of Trophic Molecules at the Lesion Site	105
4.4	Collateral Branching Versus Terminal Sprouting of Axons	106
4.5	Prospects for the Future: Role of the Cytoskeleton	107
5	Summary	108

2.1.6	Effect of Putatively Enlarged Cortical Representation of the Vibrissae in Blind Rats on the Quality of Target Reinnervation	27
2.2	Second Set of Experiments: Attempts to Reduce Collateral Axonal Branching at the Lesion Site	30
2.2.1	Effect of Extracellular Matrix Proteins Known to Foster Neurite Elongation on Axonal Branching	30
2.2.2	Time Course of Trophic Factor Expression at the Lesion Site	32
2.2.3	Effect of Neutralization of Trophic Factors at the Site of Lesion on Axonal Branching	33
2.2.4	Effect of Cell Transplantation on Axonal Branching	34
2.2.5	Effect of Transplanted Autologous Olfactory Mucosa on Axonal Branching	36
3	Results	37
3.1	Influence of the Altered Input to Axotomized Facial Perikarya on the Quality of Reinnervation	37
3.1.1	Altered Trigeminal Input to Axotomized Facial Perikarya Reduces Axonal Branching	37
3.1.1.1	Behavioral Observations	37
3.1.1.2	Lesion to the Contralateral Trigeminal Ganglion Cells Reduced the Branching of Transected Facial Axons	38
3.1.2	No Evidence for an Increased Rate of Facial Axon Elongation After Combined Facial-Trigeminal Injury	42
3.1.3	Altered Trigeminal Input Slightly Improves the Accuracy of Target Muscle Reinnervation by Regenerating Facial Axons	43
3.1.4	Electrophysiological Evidence that the Excision of the Contralateral ION Provided the Best Recovery of Synchronized Vibrissal Motor Performance	48
3.1.5	Altered Trigeminal Input Improves Motor Performance of the Vibrissal Muscles After Facial Nerve Transection and Suture (FFA)	50
3.1.5.1	Biometric Analysis of Whisking Behavior	50
3.1.6	Effect of Putatively Enlarged Cortical Representation of the Vibrissae in Blind Rats on the Quality of Target Reinnervation	55
3.1.6.1	Pre- and Postoperative Retrograde Neuronal Labeling: Despite Neurotization, the Accuracy of Reinnervation Remains Insufficient in Both Visually Normal SD Rats and in Blind SD/RCS Rats	57
3.1.6.2	Postoperative Triple Labeling: Identical Amount of Supernumerary Axonal Branches in Visually Normal SD Rats and Blind SD/RCS Rats	59
3.1.6.3	Functional Analysis of Vibrissae Movement: Poor Motor Performance in Visually Normal SD Rats, but Perfect Recovery of Whisking Behavior in Blind SD/RCS Rats	59
3.2	Attempts to Reduce Collateral Axonal Branching at the Lesion Site	62
3.2.1	Application of Extracellular Matrix Proteins Does Not Alter Axonal Branching	62
3.2.1.1	Behavioral Observations	62
3.2.1.2	Determination of Axonal Branching	65
3.2.2	NGF, BDNF, FGF-2, IGF-I, and GDNF Are Differentially Expressed in the Proximal and Distal Stumps of the Transected Buccal Branch of the Facial Nerve	67
3.2.3	Focal Application of Neutralizing Antibodies to Soluble Neurotrophic Factors Reduces Collateral Axonal Branching After Peripheral Nerve Lesion	71