PERIPHERAL NERVE REGENERATION MAHESH C. DODLA RAVI BELLAMKONDA pdf

1: Neurotree - Mahesh C. Dodla

Mahesh C. Dodla, Ravi V. Bellamkonda, in Principles of Regenerative Medicine, NATURAL NERVE GRAFTS A common source of nerve grafts is the sural nerve, which is easy to obtain, has the appropriate diameter for most grafting needs, and is relatively dispensable.

T he problem of how to bridge nerve gaps that cannot be further reduced by manipulative procedures mobilization, rerouting, stretching, etc. The results of nerve grafts in man have been disappointing, 3, 4, 5 and though improvements in technique or the use of devitalized undenatured grafts 10, 15 might yet bring better success, the prospects are so uncertain that it is indicated to explore other alternatives. Several attempts in that direction have been made in the past. Various tissues, living or fixed, as well as artificial structures, organic or inorganic, have been tried as guides for regenerating nerve fibers, mostly without significant success. As has been pointed out in a recent review of this subject by Weiss, 12 most of the former failures can be explained by errors of technique, often based on misconceptions about the mechanism of nerve regeneration. We have, therefore, continued the search for improved methods on an experimental scale, and the results are summarized in this article. On a previous occasion, 12 brief mention was made of experiments on the bridging of nerve gaps by arterial tubes filled with blood. A more detailed account of these experiments is presented in the following. The nerve ends were then fitted into a tube of artery of proper length and width by the technique described previously. Therefore, only gaps filled with whole blood will be considered here. Seven rats thus operated upon were biopsied after from 4 to 17 weeks. In the older cases, recovery of function had occurred but was decidedly inferior to that observed after end-to-end union or even after the use of frozen-dried grafts. In a number of cases, the blood-filled part of the artery had collapsed, presumably because of leakage; the wall was creased longitudinally, with practically no lumen left. A narrow strand of dense connective tissue, sometimes containing a large longitudinal blood vessel, occupied the limited central space, and regenerating nerve fibers had not been able to penetrate it. In cases in which the lumen had remained wide open, nerve regeneration across the gap had proceeded satisfactorily for varying distances, but then been impeded by islands of heavily fibrosed or areolar tissue. As already noted in previous similar experiments, 17 the orientation of the cellular strands and nerve fiber bundles was remarkably straight. On the basis of earlier experiments, 16 we thought that the formation of fibrous blocks could perhaps be prevented by increasing the fibrinolytic potency of the initial clot through the admixture of large masses of leukocytes, taken from the buffy coat stratum between red cells and plasma of centrifuged homologous blood. The ends were introduced into a matching segment of carotid artery, which was then filled with the modified blood. Except for cat F11, in which one nerve end was found at autopsy to have slipped out, the operations and subsequent recovery histories were satisfactory. Brief case descriptions follow. Gap in tibial nerve, 20 mm. At 58 days p. Active plantar flexion was definitely present at days p. At biopsy days p. The muscle weights were Since the opposite leg had been subjected to another operation, it could not be used as control for muscle weights. But the weight ratio of 3. The nerve in the area of the former gap has a characteristic pattern, differing from that observed after regeneration over short gaps, 8 but even more strikingly from that noted in gaps filled with scar tissue. It differs from the former in that it is less well oriented and contains more connective tissue, but its constitution is much nearer that of normal nerve than would ever be obtained in ordinary scar tissue. The regenerated nerve fibers are grouped into large bundles which are separated by partitions of connective tissue thicker than regular perineuria. The general direction of these bundles is longitudinal, but not straight; they interweave and give the nerve a braided appearance. The most significant difference between this type of regeneration and that in ordinary scars is that the nerve fibers are assembled into well organized strands with plenty of rather liquid light colored in Fig. The transition between this new bridge tissue and the old nerve stumps is continuous and smooth. Only at the transition to the distal stump, the tissue assumes a denser consistency, with collagen deposits inside the nerve bundles. The distal stump itself was well filled with

regenerated fibers, and sample cross sections osmic acid at various levels down to the ankle reveal abundant reinnervation and good myelinization. This deficit is evidently a result of the compression to which the fibers are subjected in the more compact fibrotic zone just mentioned, since lack of space for expansion anywhere along the course of a nerve fiber prevents the whole farther distal portion from growing in width. Longitudinal section through the whole width of the regenerated nerve portion in the region of the former gap F7 , showing braiding of nerve bundles. Gap in tibial nerve, 18 mm. It was attempted to add some buffy layer to the clotting blood through a side branch of the aorta, but upon withdrawing of the pipette most of it spilled back, so that the gap filling in this case consisted essentially of unmodified blood. At 8 weeks p. Five weeks later, the animal died. The nerve lay in a very smooth bed with no major adhesions. Upon slitting the sleeve longitudinally, a smooth cylindrical nerve segment was found to have formed over the former gap. No demarkation could be seen between this new segment and the former stumps. The weight of the calf muscles was still only 40 per cent of that of the control side, three months being too short a time for complete recovery. Nerve fiber regeneration of normal density, oriented essentially longitudinally, in bundles braided as described in the preceding case. Some endoneurial fibrosis, which had affected the diameter, but not the number, of the regenerated fibers. The distal stump was well neurotized. Gap in peroneal nerve, 10 mm. Biopsy after one year showed moderate adhesions and slight bulbous enlargement of the nerve indicative of a too tight sleeve. Muscle weight was fully recovered weights of the combined peroneus and tibialis anticus muscles: Full volume of fiber regeneration with little weaving and fairly straight longitudinal orientation Fig. Only a trace of fibrosis near entrance to distal stump; the latter fully neurotized. The superiority of this case over the two previous ones in regard to straightness of the fiber course can be correlated with the shortness of the original gap 10 mm. Portion of longitudinal section of regenerated nerve segment in the former gap region F9 , showing straight fiber course. Gap in peroneal nerve, 28 mm. A tantalum wire loop, threaded through the nerve stumps for holding purposes, was removed 8 days p. At that time, the artery appeared somewhat flattened. At 10 weeks p. At 19 weeks p. Distal two thirds of the sleeve appear partly collapsed. Weight of dorsiflexor muscles peroneus and tibialis anticus: Longitudinal folds of sleeve are evidence of the partial collapse mentioned above; however, unlike the more severe cases of collapsed sleeves described in earlier reports, 8, 14 the lumen had remained sufficiently wide to accommodate copious nerve regeneration. The fibers are again grouped into small fascicles separated by fibrous partitions and slightly braided. But, on the whole, the fiber course is remarkably straight and unconfused Fig. No fibrotic foci have developed in this case. Regeneration distance from cut to ankle was mm. Portion of longitudinal section of regenerated nerve in former gap F10 , showing straight fiber course without much braiding. The wall of the arterial sleeve can be seen. These results prove that gaps of several centimeters can be successfully bridged if the nerve fibers are offered an oriented bed of blood with augmented liquefying potency, contained in a straight tube. The regenerated nerve contains large streams of fibers, not merely those insignificant trickles occasionally found in the scars between separated, but unbridged, stumps. Since there has been no appreciable decline in the volume of regenerated fibers over gaps of nearly 3 cm. However, the technical difficulties, particularly the danger of collapse, would mount rapidly with increasing length of the free portion of the sleeve. It was mainly to meet these difficulties that we began to modify the method in the following manner. Since regenerating axons, in turn, tend to advance along Schwann cell strands, extension of these tissue culture experiments to problems of actual nerve repair suggested itself. We therefore supplemented the simple tubulation technique described above by including in the blood bridge large numbers of thin, parallel, longitudinally oriented artificial fibers of various kinds, for the double purpose of giving the link greater consistency and of giving the Schwann cells and axons oriented pathways leading straight from stump to stump. After this had firmly clotted, the whole preparation was used much as if it were a nerve graft. A segment was excised from the peroneal nerve so as to leave a gap of ca. No further means of attachment were used. The 24 animals included in this series were sacrificed between 7 and 77 days p. Our main purpose was to study the microscopic picture; all bridges except those containing glass fibers could be sectioned, as the fibers either dissolved or softened during the

histological treatment. No motor recovery had occurred, and stimulation of the distal stumps at autopsy gave no evidence of sensory fiber regeneration. Functionally, these cases were complete failures. Microscopic examination revealed the reason, which was a purely technical one. The artificial fiber core had failed to form an intimate union with at least one, and often both, stumps. It was separated from them by a small, but distinct, cavity filled with liquid. As neither spindle cells nor nerve fibers cross liquid gaps, no organic junction had been effected. The explanation of this non-union lies in the relative rigidity of the fiber core. As the blood menstruum in the sleeve became dissolved, the fibers were forced closer together into a rather stiff bundle, which then acted as a mechanical unit. While the arterial sleeve was elastic, the fiber core was not. The movements of the animal, therefore, caused continual slight displacements between the fiber bundle and the nerve stumps, and any incipient tissue links were thus constantly ruptured before they had a chance to become consolidated. The inset could thus become firmly attached to one stump or the other, but not to both. In those cases in which the graft had become firmly fused with the proximal stump, it was invaded by regenerating nerve fibers in various ways and degrees. When the filaments of the core were too tightly packed, no tissue penetrated between them. When spaced more loosely, the interstices became invaded by a tissue composed of blood cells, mesenchyme, Schwann cells, nerve fibers and serous spaces, in varying ratios. Textile rayon evoked in all cases a strong foreign body reaction with small-cell infiltration, liquid exudates, and poor growth of organized tissue. There was little or no liquefaction, and the regenerating tissue adhered firmly to the fiber surfaces. The cells and axons followed strictly longitudinal courses, not only where they were in direct contact with the guide fibers, but also in the intervening meshes. In some cases, the interior of the fiber bundle had remained devoid of cells, while there was ample growth in the more superficial layers, and these, in turn, were surrounded by a layer of pure regenerated nerve tissue, which filled the space between the fiber core and the wall of the sleeve.

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2: Publications Authored by Ravi V Bellamkonda | PubFacts

Peripheral Nerve Regeneration Using a biomaterial approach and using biomimetic 3D scaffold that draw their design inspiration from principles of contact guidance, haptotaxis/ chemotaxis, regeneration of injured nerves are promoted.

However, nerve grafts have many limitations, such as, availability of donor nerve grafts, and loss of function at donor site. To overcome these problems, we have used a tissue engineering approach to design three-dimensional 3D agarose scaffolds containing gradients of laminin-1 LN-1 and nerve growth factor NGF to mimic in vivo conditions to promote nerve regeneration in rats. To determine the effect of LN-1 gradients on neurite extension in vitro, dorsal root ganglia DRG from chick embryos were cultured in 3D hydrogels. A gradient of LN-1 molecules in agarose gels was made by diffusion technique. Anisotropic scaffolds with three different slopes of LN-1 gradients were used. Isotropic scaffolds with uniform concentrations of LN-1, at various levels, were used as a positive control. DRG cultured in anisotropic scaffolds with optimal slope of LN-1 gradient extended neurites twice as fast as DRG in optimal concentration in isotropic scaffolds. Also, in the anisotropic scaffolds the faster growing neurites were aligned along the direction of LN-1 gradient. To promote nerve regeneration in vivo, tubular polysulfone guidance channels containing agarose hydrogels with gradients of LN-1 and NGF anisotropic scaffolds were used to bridge mm nerve gaps in rats. Nerve autografts were used as positive controls and isotropic scaffolds, with uniform concentration of LN-1 and NGF, were used as negative controls. After 4-months, the rats were sacrificed and nerve histology was done to test for nerve regeneration. Only anisotropic scaffolds and nerve autografts contained evidence of axonal regeneration. Both groups had similar numbers of myelinated axons and similar axonal-diameter distribution. However, nerve graft group performed better in functional outcome as measured by relative gastrocnemius muscle weight RGMW and electrophysiology. Optimization of performance of anisotropic scaffolds by varying the LN-1 and NGF concentration gradients might lead to development of scaffolds that can perform as well as nerve auotgrafts for nerve regeneration over long nerve gaps. Bellamkonda, Ravi; Committee Member: English, Arthur; Committee Member: Garcia, Andres; Committee Member: LaPlaca, Michelle; Committee Member: Agarose hydrogels, Laminin, Nerve growth factor, Nerve regeneration Publisher: Georgia Institute of Technology Year: Sorry, we are unable to provide the full text but you may find it at the following location s:

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3: Principles of Regenerative Medicine : Robert M. Nerem :

Mahesh C. Dodla, Ravi V. Bellamkonda, in Principles of Regenerative Medicine, Collagen Gels. Collagen gels and filaments have been used to promote PNS regeneration (scaffolds with collagen filaments will be discussed later in the anisotropic scaffolds section).

Developing Brain Cancer Therapies Using nanocarrier encapsulation of drugs efficacious treatments for glioblastoma multiforme GBM a major form of brain cancer has been successfully developed. The generality of this approach is being currently evaluated in metastatic tumors of other tissue origin. Nanocarrier technology is also exploited to demarcate tumor margins to aid neurosurgeons in surgical removal of brain tumors. Bellamkonda group have shown that tissue-energized scaffolds are comparable to the autografts in their performance. A wealth of information is also generated from these studies with respect to the response to topographical cues as well as cellular and molecular mechanisms that take place in the regeneration microenvironment. More recently, strategies based on an immunological approach has been adopted to facilitate the regeneration process. Creating an anti-inflammatory macrophage phenotype subsequent to peripheral nerve injury has shown to favorably bias the regenerative process. Another active area in this realm is the fabrication of multi-channel devices for implantation to aid restoration of lost function in amputees. Brain Electrode Interfacing The major focus in the are a of brain-electrode interfacing is to unravel the reasons for the failure of the electrodes in a short period of time after implantation. To understand the causation of the failure, an investigation is carried out using a multidisciplinary approach. The sequences of cellular and molecular events that follow the electrode implantation are examined and a correlation is made to the ability to record from these devices. This should lead to predicting, at an earlier time point, the potential for these devices to fail. Also, novel electrode arrays are designed to overcome some of the drawbacks of the current electrodes. Our recent work has brought to light the role of compromised blood brain barrier BBB and the failure of implanted electrodes. Future strategies will focus on implementing strategies to cause healing to increase the life of the electrode interfaces. Correlation of mRNA expression and signal variability in chronic intracortical electrodes. Frontiers in Bioengineering and Biotechnology. Engineering challenges for brain tumor immunotherapy. Bacterial carriers for glioblastoma therapy. Molecular Therapy - Oncolytics. Enrichment of endogenous fractalkine and anti-inflammatory cells via aptamer-functionalized hydrogels. Guiding intracortical brain tumour cells to an extracortical cytotoxic hydrogel using aligned polymeric nanofibres. Relationship between intracortical electrode design and chronic recording function. The impact of chronic blood-brain barrier breach on intracortical electrode function. Effect of modulating macrophage phenotype on peripheral nerve repair. Anti-invasive adjuvant therapy with imipramine blue enhances chemotherapeutic efficacy against glioma.

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4: Bioengineered Scaffolds for Peripheral Nerve Regeneration

Mahesh Chandra Dodla BIOENGINEERED SCAFFOLDS FOR PERIPHERAL NERVE REGENERATION Approved by: Dr. Ravi V. Bellamkonda.

Current Issues in U. Nerem Anthony Atala, M. Atala is a practicing surgeon and a researcher in the area of regenerative medicine. His current work focuses on growing new human cells, tissues and organs. Atala is a recipient of the US Congress funded Christopher Columbus Foundation Award, bestowed on a living American who is currently working on a discovery that will significantly affect society, and the Gold Cystoscope Award for advances in his field. Atala was named by Scientific American as a Medical Treatments Leader of the Year for his contributions to the fields of cell, tissue and organ regeneration. In , he was named by Fast Company magazine as one of 50 people who "will change how we work and live over the next 10 years. A Time Magazine poll ranked Dr. Atala as the 56th most influential person of the year in Esquire Magazine in named Dr. Atala one of the 75 most influential persons of the 21st century. Fast Company Magazine named Dr. Atala one of Most Creative People in Business in Atala was featured in U. Atala has led or served several national professional and government committees, including the National Institutes of Health working group on Cells and Developmental Biology, and the National Institutes of Health Bioengineering Consortium. Atala heads a team of over physicians and researchers. Ten applications of technologies developed in Dr. He is the editor of nine books, including Minimally Invasive Urology, Methods of Tissue Engineering, Principles of Regenerative Medicine, and Foundations of Regenerative Medicine, and has published more than journal articles and has applied for or received over national and international patents. Lanza received his B. He also worked closely and coauthored a series of papers with the late Harvard psychologist B. Skinner and heart transplant pioneer Christiaan Barnard.

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74 Peripheral Nerve Regeneration Ravi Bellamkonda Mahesh C. Dodla 75 Dental Tissue Engineering Pamela Yelick Yan Lin 76 Innovative Regenerative Medicine Approaches to Skin Cell-Based Therapy for Patiens with Burn Injuries Jorg Gerlach Steven E. Wolf Christa Johnen Bernd Hartman.

6: Guides for Nerve Regeneration Across Gaps : Journal of Neurosurgery

Mahesh C. Dodla, Ravi V. Bellamkonda rat peripheral nerve regeneration through artery-including silicone tubing. Severed Peripheral Nerves of Monkeys. Journal.

7: Bioengineered Scaffolds for Peripheral Nerve Regeneration - CORE

Dodla MC, Bellamkonda RV. () Differences between the effect of anisotropic and isotropic laminin and nerve growth factor presenting scaffolds on nerve regeneration across long peripheral nerve gaps.

8: results in SearchWorks catalog

Several advances in nerve cell culture, development of new biomaterials, and genetic techniques have led to the introduction to innovative techniques for nerve regeneration. Analytically, natural.

9: Bellamkonda Lab

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13 Mahesh C. Dodla, Vivek J. Mukhatyar, Ravi V. Bellamkonda, Principles of Regenerative Medicine, , CrossRef 14 Xu Jiang, Shawn H. Lim, Hai-Quan Mao, Sing Yian Chew, Current applications and future perspectives of artificial nerve conduits, Experimental Neurology, , , 1, 86 CrossRef.

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