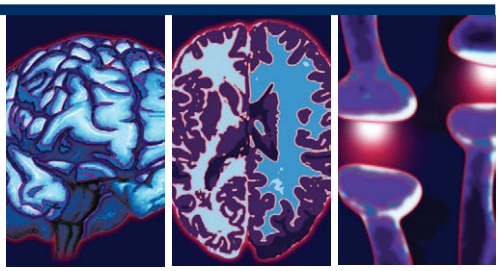
Review



Terminolateral Neurorrhaphy between Somatic Nerve and Autonomic Nerve

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Abstract

Background

In peripheral nerve injury, terminolateral neurorrhaphy is a promising approach for repairing nerve. However, this nerve repair method was confined to somatic nerve system in previous studies. At present, there have been a few studies on the nerve regeneration following terminolateral neurorrhaphy between two different characteristics of somatic nerve and autonomic nerve in the peripheral nervous system.

Methods and Findings

We searched the relevant literature about terminolateral neurorrhaphy between somatic nerve and autonomic nerve in the PubMed database, and only 5 related studies were retrieved. Among the five studies, four studies were animal experiments, and one study was concerned with the clinical use of terminolateral neurorrhaphy. According to these five articles, we reviewed and analyzed the animal models, the advantages and the mechanism of nerve regeneration of terminolateral neurorrhaphy between somatic nerve and autonomic nerve with different characteristics in the peripheral system in this review.

Conclusion

Terminolateral neurorrhaphy of somatic nerve and autonomic nerve for nerve repair not only can promote recipient nerve function recovery, but also does not deteriorate the donor nerve function simultaneously. Terminolateral neurorrhaphy of autonomic nerve and somatic nerve is a novel and original concept that would cause great interest in reconstructive surgeons and neuroscientists.

Keywords

Terminolateral neurorrhaphy; Somatic nerve; Autonomic nerve; Nerve regeneration

Introduction

Terminolateral neurorrhaphy is a nerve anastomosis technique, which involves the distal end of the damaged recipient nerve to be anastomosed to the lateral side of the adjacent, intact and healthy donor nerve, inducing donor nerve collateral sprouting and axon regeneration into the recipient nerve, realizing nerve regeneration of the recipient nerve and reinnervation of target organ, and that the adverse effects on the donor nerve was reduced to a minimum [1].

The history of terminolateral neurorrhaphy can be divided into three stages [2]. The first stage is the initial stage. Letievanto proposed the original concept of terminolateral neurorrhaphy

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in a book [3]. Despres carried out terminolateral neurorrhaphy in patients for the first time [4,5]. However, many researchers regarded Kennedy as the first author to report the terminolateral neurorrhaphy of peripheral nerve in the clinical practice, because he reported a case through facial nerve and spinal accessory nerve end-to-side anastomosis for treatment of facial spasm [6-9]. The second stage is the early application stage of terminolateral neurorrhaphy. In the first half of the twentieth Century, researchers reported a number of clinical studies about terminolateral neurorrhaphy [10-12]. Nerve regeneration has been confirmed to occur by morphological observation in experimental studies of animal models after terminolateral neurorrhaphy [13,14]. However, there is no enough understanding about the main ways of nerve regeneration and the mechanism of collateral sprouting of donor axon after terminolateral neurorrhaphy, leading to the donor nerve deliberately severely injured and the technology has not been applied to clinical in the next 50 years [15]. The third stage is the re-discovery of terminolateral neurorrhaphy for nerve repair. Viterbo, *et al.* [16-18] and Lundborg, *et al.* [19] published the experimental studies, discovering that axons regeneration could occur through collateral sprouting originated from intact donor nerve fibers without damage to the donor nerve, which was regarded as the ''re-discovery'' of terminolateral neurorrhaphy. Aiming at confirming the effectiveness of nerve regeneration following terminolateral neurorrhaphy, different investigation techniques were used in various experimental models of a number of studies were published following Viterbo and Lundborg in the second half of the nineties [20-23].

The peripheral nervous system includes the peripheral autonomic nervous system and the peripheral somatic nervous system [24]. However, terminolateral neurorrhaphy for nerve repair had been confined to somatic nerve in previous studies until Gao, *et al.* [25] reported terminolateral neurorrhaphy between somatic nerve and autonomic nerve, which has different characteristics in the peripheral nervous system.

Methods

We searched the relevant literature about terminolateral neurorrhaphy between somatic nerve and autonomic nerve in the PubMed database following the query: ((End to side neurorrhaphy) OR terminolateral neurorrhaphy) AND autonomic nerve) AND somatic nerve and only 5 related studies were retrieved by July. Among the five studies, four studies were animal experiments, and one study was concerned with the clinical use of terminolateral neurorrhaphy. According to these five articles, we reviewed and analyzed the animal models, the advantages and the mechanism of nerve regeneration of terminolateral neurorrhaphy between somatic nerve and autonomic nerve with different characteristics in the peripheral system in this review.

■ Experimental models of terminolateral neurorrhaphy of Autonomic- Somatic Nerve

The L4 ventral root (VR) belongs to somatic nerve and the L6 VR is a mixed nerve and has two main branches, which composed of autonomic and somatic nerves [26]. The postganglionic parasympathetic nerve arising from L6VR innervate the bladder, rectum and penile erection after the pelvic parasympathetic neuron exchanges in the major pelvic ganglion(MPG), and the pudendal somatic nerve of the L6VR innervate the striated muscles and sphincters involved in micturition, defecation and in the male erection and ejaculation, respectively [27]. The pelvic preganglionic parasympathetic nerve (PPN) is completely composed of autonomic nerve fibers derived from L6 and S1 and synapses with postganglionic parasympathetic neurons, which is called as MPG that releases the nerve fibers to innervate the bladder, rectum, and penile erection [28-31]. Gao, *et al.* [32] established an experimental model through intradural terminolateral neurorrhaphy between somatic nerve and autonomic nerve for repairing nerve and reconstructing bladder function, in which the left L6VR was anastomosed to the left L4VR that maintain L4VR intact in rats.

To verify whether the artificial reflex pathway had been established, Gao, *et al.* injected the tracers into the MPG and sciatic nerve (SN) respectively to perform the retrograde nerve tracing study. SN is mainly composed of L3–L5 spinal nerves [33]. In the terminolateral neurorrhaphy rats, the ventral roots and the dorsal roots of L6 and S1 were intersected at first, and then the left L6VR was anastomosed to the lateral face of the left L4VR. Hence, the PPN of terminolateral neurorrhaphy consisted of pure nerve fibers of L6VR, so that the exact quantity of nerve fibers regeneration can get and the contraction of the bladder can only be achieved by establishing the artificial reflex pathway.

Retrograde nerve tracing showed that the artificial reflex pathway between left L6VR (recipient nerve) and the left L4VR (donor nerve) had been established, and nerve fibers of L4VR could regenerate mainly through axons collateral sprouting. The morphological and ultra-structural observation of the regenerated recipient nerve indicated the obvious axonal regeneration of the recipient nerve at the distal end of the anastomosis following terminolateral neurorrhaphy. The nerve morphological observation showed that the numbers of myelinated axons at the L4VR distal end of the anastomosis was similar with those of the L4VR proximal end of the anastomosis, indicating that terminolateral neurorrhaphy did not cause significant damage to the donor nerve. When the left L4VR proximal to anastomosis was stimulated by bipolar electrode, bladder pressure could significantly increase, which indicated that nerve fiber stimulation signals could transmit to the bladder through regenerative nerve and initiate contraction, inducing micturition in rats. Dong, *et al.* [34,35] sutured the left L6VR to the left L4VR through intradural erminolateral neurorrhaphy to reconstruct anorectal and erectile function respectively. His studies also demonstrated that nerve regeneration could be achieved through axons collateral sprouting following terminolateral neurorrhaphy between somatic nerve and autonomic nerve and the regenerated nerve could re-innervate the target organ without apparent adverse effect to donor nerve by retrograde nerve tracing, morphological and histological observation, anorectal manometry assessment and evaluation of the erectile function in two different researches.

Gao, *et al.* [32] and Dong, *et al.* [34,35] demonstrated that nerve regeneration and functional recovery following terminolateral neurorrhaphy between somatic nerves and autonomic nerves with different characteristics was feasibility and the donor nerve function without getting impaired. This is a novel and original point of view, which provided a new way for the repair of damaged peripheral nerve injury in the future without damaging the donor nerve function.

■ The advantages of terminolateral neurorrhaphy of autonomic- Somatic nerve

The advantage of terminolateral neurorrhaphy has been widely recognized, while this method of never anastomosis was confined to somatic nerves in previous studies [36-38]. Neurogenic voiding dysfunction and bowel dysfunction resulting from neural tube defects and spinal cord injury (SCI) has been a worldwide medical problem. In the past decades, many clinicians tried to apply various methods for the treatment of neurogenic bladder and bowel dysfunction including drugs, intermittent catheterization, electronic stimulation of sacral nerve roots and so on [39-45]. However, the effects of these efforts were not ideal.

Xiao and associates established the skin-central nervous reflex pathway system for the treatment of neurogenic bladder through end-to-end anastomosis of left L4/L5 ventral VR (somatic nerves) to L6/S2 VR(autonomic nerve) in rats and cats, respectively[46, 47]. Peters [48] and Xiao [49,50] demonstrated that the skin-central nervous reflex pathway system following end-to-end anastomosis of L5 VR (somatic nerves) to S2/S3 VR (autonomic nerve) could recover controllable voiding function in the clinical trial. However, this method of nerve anastomosis had obvious injury to the donor nerve and affects the donor nerve of somatic motor function. Zheng, *et al.* [51] and Lin, *et al.* [52] established an abdomen-to-bladder reflex pathway for the treatment of neurogenic bladder caused by SCI through end-to-end anastomosis of L5VR or T12VR to S2VR by autogenous nerve grafting to reconstruct bladder function. However, this method of anastomoses inevitably sacrificed a segment of nerve, causing donor nerve injury.

Terminolateral neurorrhaphy is a surgical technique of nerve anastomosis, which involved the damaged recipient nerve that is anastomosed to the lateral side of the adjacent, intact and healthy donor nerve, inducing donor nerve regeneration through axons collateral sprouting and into the distal stump of recipient nerve to realize the function of recipient nerve recovery and re-innervation of target organs, without obvious side effects on the donor nerve meanwhile.

In conclusion, terminolateral neurorrhaphy of somatic nerve and autonomic nerve has the following advantages. At first, when there is long nerve segment defect, a damaged recipient nerve is anastomosed to the lateral side of the adjacent, intact and healthy donor nerve through end-to-side anastomosis, which not only can restore the function of recipient nerve but also prevent donor function atrophy of target organ. Secondly, when compared with conventional nerve grafts,

this approach does not cost the donor function when nerve grafting. Thirdly, this method of anastomosis does not require the removal of the donor nerve root, which is important to protect the function of donor nerve in patients with spina bifida or SCI. Therefore, the view of achieving the regeneration of autonomic nerve and the re-innervation of target organs without impairing the function of the donor somatic nerve is attracting much attention in the field of department of neurosurgery.

■ The mechanism of nerve regeneration of terminolateral neurorrhaphy autonomic -somatic nerve

Recent literature evidence suggested that the mechanism of nerve regeneration following terminolateral neurorrhaphy comes mainly from two aspects. One way is that the regenerative nerve derived from collateral sprouting from the intact donor nerve [53-55]. The other is that regenerated nerve derived from terminal sprouting of donor nerve due to the damage to the donor nerve during suturing process [56-58]. Zhang, *et al.* [59] and Hayashi, *et al.* [60] demonstrated that the nerve regeneration through the terminolateral neurorrhaphy originated from the collateral sprouting from the intact donor nerve by using immunofluorescence tracing technique. However, Hastert, *et al.* [61] founded that nerve regeneration not only originated from collateral sprouting from non-injurious donor nerve, but also originated from terminal sprouting from the damaged donor nerve when retrograde nerve tracing of neurons performed with DiI and FluoroGold to reveal the origin of regenerated axons through sciatic nerve in a rat model.

In order to prove that whether the artificial reflex pathway have been established and the mechanism of nerve regeneration through terminolateral neurorrhaphy between the L4VR (somatic nerve) and the L6VR (autonomic nerve), Gao, *et al.* [32]and Dong, *et al.* [34,35] injected Fast Blue (FB) and Fluoro-Gold (FG) into the SN and MPG, respectively. FB was blue labeling the cytoplasm, while FG was yellow labeling both the cytoplasm and nucleus under the excitation of ultraviolet light [62]. The FG-FB was yellow-blue double labeling the whole cell under the ultraviolet filter set [63]. FG single-labeled neurons appeared alone, which indicated that regenerated nerve fibers originated from terminal sprouting from injured donor nerve following terminolateral neurorrhaphy [64]. The appearance of FG-FB double labeling neurons indicated that regenerated nerve fibers derived from collateral sprouting from the donor nerve [65]. Gao, *et al.* [32] and Dong, *et al.* [34,35] found that three kinds of labeled neurons of FB, FG and FB-FG all appeared in the L4 left ventral horn in the retrograde nerve tracing study following terminolateral neurorrhaphy. The results demonstrated that the artificial reflex pathway between somatic nerve and autonomic nerve have been established through terminolateral neurorrhaphy. The results also suggested that there were two mechanisms that axons collateral sprouting and axons terminal sprouting, when donor somatic nerve grew into the recipient autonomic nerve following terminolateral neurorrhaphy. However, the number of FG-FB double-labeled neurons was more than that of the FG single-labeled neurons, indicating that donor nerve grew into and replaced the recipient nerve, which was mainly derived from axonal collateral sprouting.

Moreover, the donor nerve could grow into and replace the recipient nerve through terminolateral neurorrhaphy, which is related to the following factors. Firstly, the slight damage to the donor nerve led to the release of some nerve growth factors which promoted regeneration during the nerve anastomosis [66]. The use of helicoid coaptation greatly increased the surface area of donor nerve and the recipient nerve, which contributed to nerve regeneration [67]. In addition, there are other factors that also influenced nerve regeneration including neurotrophic factors, timing of coaptation and the number of Schwann cells at the anastomosis site [68].

■ Epineurium or perineurium window

Before performing terminolateral neurorrhaphy, whether or not open a window on the perineurium or epineurium of the donor nerve which is necessary, and has been extensively discussed in the previous literature [69,70]. In fact, when there is no injury to the donor nerve, nerve regeneration can occur following end-to-side anastomosis, but several experimental studies have shown that when the donor nerve had a fenestration, the effect of nerve regeneration was better [71-74]. Although there are still controversies over whether fenestration can damage the donor nerve, many studies have confirmed that the fenestration of the epineurium can cause a slight damage to the donor nerve, but does not affect the donor nerve function [75-77].

Gao [32] and Dong, *et al.* [34,35] used the epineurium window during the intradural end-to-side microanastomosis between L4VR and L6VR. The appearance of unmyelinated and myelinated axons in the regenerated nerve fibers following terminolateral neurorrhaphy demonstrated that the somatic nerve could regenerate and grow into the distal end of the autonomic nerve. The results of the morphology and wet weight of muscle dominated by donor nerve showed there was no effect on the donor nerve function. However, because of the lack of controlled studies, it is not known whether the nerve regeneration following terminolateral neurorrhaphy between autonomic nerve and somatic nerve is superior or not. Hence, the further studies are needed.

The future

The nerve regeneration following terminolateral neurorrhaphy of somatic nerve and autonomic nerve and achieving re-innervation of target organs without sacrificing the function of the donor nerve is a novel and remarkable view. At present, there is no clinical report of terminolateral neurorrhaphy between somatic nerve and autonomic nerve, except that Souza Trindade, *et al.* [78] reported a case that using four sural nerve grafts and terminolateral neurorrhaphy to reconstruct bilaterally femoral and the cavernous corpus reinnervation, through femoral nerve and the dorsal penile nerve regeneration. Furthermore, because of the different regeneration abilities of nerve fibers in humans and rats, some nerve growth factors are used to promote axons collateral sprouting and penetrating ability to improve the effect of nerve regeneration in the further study.

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Conflicts of interest

The authors have no conflicts of interest.

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