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Liquid metal as reconnection agent for peripheral nerve injury

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Abstract This study demonstrated an unconventional way to cure peripheral nerve injury (PNI) with liquid metal gallium employed as the reconnection agent. In vivo experiments were performed, in which transected sciatic nerve of mouse was reconnected by liquid metal gallium. The nerve signals detected was found to be almost the same as those from the complete nerve, where the negative bursting firing caused by PNI was absent on the neural discharge curve after nerve-reconnection surgery. Meanwhile the atrophy tendency of gastrocnemius muscle was distinctly procrastinated according to the results of pathological examinations, which showed fibrillation potentials emerged immediately for mice with PNI but did not emerge until the third month for those received nerve-reconnection surgery. Furthermore, physical properties of gallium were studied, showing that its impedance was slightly influenced by the frequency of transmitted signal and the temperature, which confirmed the stability of gallium in future clinical usage. This technology is expected to perform well in clinical surgery for PNI and even central nervous system injury in the coming time.

Keywords Peripheral nerve injury · Liquid metal · Nerve repair · Neuroprosthetics · Muscle atrophy

1 Introduction

Peripheral nerve injury (PNI) is an increasing and common entity for movement disorder [1–4], and the resulted partial or complete functional loss continues to be a significant clinical challenge [5, 6]. PNI is generally caused by accidents, disease, long term bad habits and overload labor. The resulted muscle atrophy and long-term disability requires extremely complex surgical treatments, but unfortunately not all can be managed under surgical intervention [7]. With the developments on anatomy and pathophysiology of peripheral nerve system (PNS), the repair and regeneration of PNI were found to be dependent on the position and extent of damage [8]. Conventional cases of PNI are described in Fig. 1, where four grades are arranged from left to right according to the severity of resulted functional loss. Once degeneration processes occurred, the caused functional disability will be theoretically irreversible [9–11].

The majority of recent clinical strategies and research efforts for PNI has emphasized neurorrhaphy, nerve entubulation, nerve graft and nerve transfer. Neurorrhaphy is normally employed for small nerve gaps (<5 mm), where opposing nerve stumps of the detached verve are reconnected by suturing the nerve epineurium or perineurium [12–14]. However, for larger defects, excessive tension emerges over the repaired nerve, resulting in neuralgia and neuroma [15, 16]. When a significant nerve gap exists, a nerve entubulation or nerve graft could be carried out [17, 18], including autograft and allograft, depending

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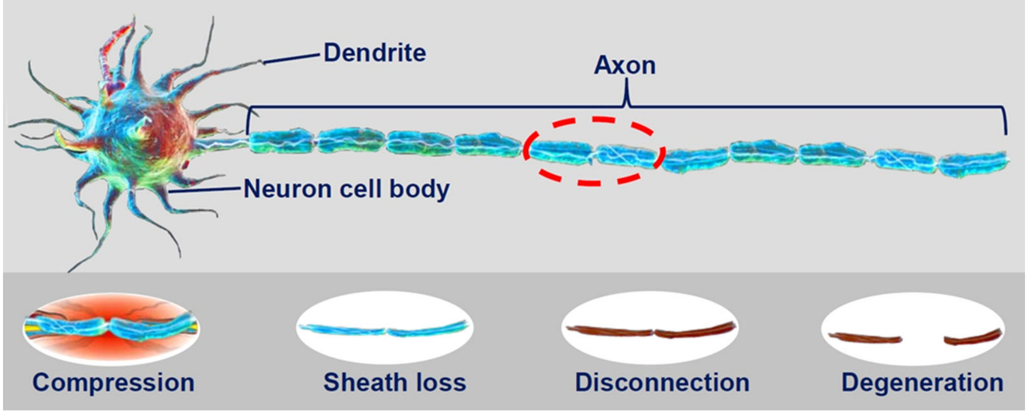

Fig. 1 (Color online) A schematic description of different PNI cases. Nerve compression syndrome (compression neuropathy, entrapment neuropathy) is caused by direct pressure on a single nerve, producing symptoms such as pain, tingling, numbness, and muscle weakness. The process of sheath loss insulating nerves is demyelination, as the hallmark of some neurodegenerative autoimmune diseases. The disconnection refers to the blocking of neural signal circuit, with or without the physical cutting off. Axons regenerating grows through an extracellular environment elaborated by glia cells and other nonneuronal cells of the nerve stump, along with Schwann cells proliferated

on the donor nerve. As an alternative and graft-free intervention, nerve transfer connects the proximal nerve stump directly to target muscle belly, and is only used in special situations in which incomplete regeneration is anticipated [19]. Moreover, nerve transfer operation shows poorer effects than neurorrhapy and nerve graft.

As generally known, neural signals are transmitted in the form of electric current called action potential, firstly reported in late nineteenth century [20]. In the nervous system, including central nervous system (CNS) and PNS, the electricity is generated and transmitted by changing concentrations of ions including K^+, Na^+ and Ca^{2+}, which results in polarization or depolarization of the nerve axon, producing sudden and rapid sequence of induced voltage changes (action potential) [21]. There has been a significant effort dedicated to developing conductive agents for PNI that have resulted in encouraging regeneration and some degree of functional recovery [22–26]. Wilson and Jagadeesh [27] reported that electrical stimulation could significantly accelerate the regeneration of injured nerve after examining a large number of animal experiments. Since then, there has been a large focus on the use of conductive materials in neural tissue engineering [28–35]. And researchers hope to develop a novel material that can meet both the conductivity demands of nerve tissue and the requirements of tissue engineering, including biocompatibility, biodegradability and so on. Electroconducting polymers, such as polypyrrole (PPY), polyaniline (PANI), and polyphosphazene (PZ) have been studied and show the excellent biocompatible property [36, 37]. But the disadvantages of those polymers are the discharge of acidic degradation products, poor process ability and early failure of mechanical features during degradation [38]. Liquid metal has already been the subject of enough research to say with near-certainty that it is truly biocompatible, which gives it hope for applications within a living body. Compared with conductive polymers and Riger's Solution (a conventionally used conductor solution), the resistivity of liquid metal is several orders lower, which can efficiently avoid the attenuation of electroneurographic signals. The frequencies of most electroneurographic signals are below 10 kHz [39–42], and the resistance of liquid metal is relatively stable in a wide range of incoming frequency. While for other soft conductors, like conductive polymers and Riger's Solution, the resistance and reactance are highly affected by frequency [43–46]. Therefore, we tried to use liquid metal to reconnect the transected sciatic nerve, where capillary silicone tube was used as the encapsulation.

As an emerging multifunctional material, room-temperature liquid metal recently draws world-wide attentions due to its intriguing and unexpected properties, including low melting point (MP), infinite stretchability [47], excellent electrical conductivity, chemical stability and good biocompatibility, which make liquid metal suitable for applications on reconnection of transected nerve. In previous work, we reported the in vitro study of eutectic GaInSn alloy (67 % Ga, 20.5 % In and 12.5 % Sn by volume) as connecting channel for transected sciatic nerve [48]. It was found that, after electrical stimulus, the measured induced signal from reconnected nerve was similar to that from the intact sciatic nerve. Here, the liquid metal gallium was employed as a novel reconnection agent to treat the PNI on a mouse with sciatic nerve transected, approved by the Ethics Committee of Tsinghua University, Beijing, China under contract (SYXK (Jing) 2009-0022). Neurological electrophysiology measurements and biopsy study were conducted to estimate the surgery effect. Whilst, electrical and thermal properties of this material