Can lithium enhance the extent of axon regeneration and neurological recovery following peripheral nerve trauma?

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Abstract

The clinical "gold standard" technique for attempting to restore function to nerves with a gap is to bridge the gap with sensory autografts. However, autografts induce good to excellent recovery only across short nerve gaps, in young patients, and when repairs are performed a short time post nerve trauma. Even under the best of conditions, < 50% of patients recover good recovery. Although many alternative techniques have been tested, none is as effective as autografts. Therefore, alternative techniques are required that increase the percentage of patients who recover function and the extent of their recovery. This paper examines the actions of lithium, and how it appears to trigger all the cellular and molecular events required to promote axon regeneration, and how both in animal models and clinically, lithium administration enhances both the extent of axon regeneration and neurological recovery. The paper proposes more extensive clinical testing of lithium for its ability and reliability to increase the extent of axon regeneration and functional recovery.

Key Words: anastomosis; axon regeneration; lithium; nerve crush; nerve gaps; nerve repair; nerve trauma; neurological recovery; Schwann cells

Introduction

Sensory autografts are the clinical "gold standard" technique for repairing nerves with a gap (Houschyar et al., 2016; Hoben et al., 2018; Kornfeld et al., 2019; Pan et al., 2020). However, they lead to good to excellent functional recovery only for gaps < 3–5 cm (Terzis and Kokkalis, 2008; Karabeg et al., 2009; Hoben et al., 2018; Pan et al., 2020), repairs performed < 3–5 months post-trauma (Matejcik and Penzesova, 2006; Terzis and Kokkalis, 2008), and patients < 20–25 years old (Matejcik and Penzesova, 2006; Terzis and Kokkalis, 2008; Karabeg et al., 2009). Further, even under the best conditions, less than 50% of patients recover good to excellent functional recovery. As the values of any two or all three of these variables increase, recovery is generally limited to none (Ruijs et al., 2005; Terzis and Kokkalis, 2008; Grinsell and Keating, 2014). Although many alternative techniques have been tested, none is more effective than autografts, and the rate of functional recovery has not improved in about 70 years (Sunderland, 1951; Ruijs et al., 2005). Therefore, novel techniques are required that increase the percentage of patients who recover and the extent of their recovery.

A good candidate for increasing the extent of functional neurological recovery must: (a) activate a complex cascade of coordinated neuron gene expression, (b) promote the translation of local proteins in axons and their anterograde transport along the axon, (c) trigger the assembly of cytoskeleton and membranes within the nerve growth cone, and (d) activate a cascade of Schwann cell events. One compound that meets these criteria is lithium.

Search Strategy and Selection Criteria

Animal model and clinical studies published in English from 1980 to August 2021 were searched on the Google Scholar and PubMed using the following keywords: lithium, axon regeneration, neurological recovery, recovery of function, nerve trauma, Schwann cells, nerve repair, nerve gaps, anastomosis, allografts, nerve crush, nerve conduits, autologous nerve grafts, sensory nerve grafts, nerve gap length.

Lithium-General Background

Lithium has a 50-year history of use as the principal drug for treating depression, especially bipolar and depressive mood disorders (Pies, 2002; Gould et al., 2004). Lithium is also effective in treating neurodegenerative disorders such as Huntington (Senatorov et al., 2004; Raja et al., 2015), Alzheimer's (Matsunaga et al., 2015), and Parkinson's diseases (Moors et al., 2017), amyotrophic lateral sclerosis (van Eijk et al., 2017), and experimental autoimmune encephalomyelitis (De Sarno et al., 2008). Additional roles of lithium include increasing cerebral blood flow (Zhong et al., 2006), and when administered immediately following a transient ischemic brain injury, it provides neuroprotection and improved neurological outcomes (Silachev et al., 2015). Lithium exerts an anti-inflammatory effect on the cerebral tissue (Basselin et al., 2007), acts as an anti-oxidant (Jornada et al., 2011), supports protein homeostasis, neurogenesis, synapse maintenance, and has anti-apoptotic properties (Chuang, 2005). Of greatest relevance to this review, lithium activates phosphoinositide 3-kinase (PI3K) (Dong et al., 2014), regulates the activity of glycogen synthase kinase-3 (GSK3)

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(Wada, 2009; Costemale-Lacoste et al., 2016), the expression of c-Jun (Chen et al., 2003), and Bcl-2 (Manji et al., 2000; Dwivedi and Zhang, 2014), and promotes angiogenesis (Liu et al., 2019).

Lithium in Central Nervous System and Peripheral Nervous System Injuries

Following mouse optic nerve (Cho and Chen, 2008) and rat spinal cord injuries, the injection of lithium enhances axon regeneration (Yick et al., 2004; Su et al., 2014; Zhang et al., 2018b) and the extent of functional recovery (Fu et al., 2014; Zhang et al., 2018a). In a rat model, lithium administration improves functional motor recovery after ventral root avulsion and reimplantation (Fang et al., 2016). Also, in rats, injecting lithium into a conduit bridging sciatic nerve gaps increases Schwann cell density significantly, and the distance axons regenerate across the gap (Lin et al., 2013). Following a mouse facial nerve crush, lithium administration stimulates the expression of myelin genes, restores myelin structure, and accelerates the recovery of whisker movements *vs*. control animals (Makoukji et al., 2012; Chen et al., 2016). Thus, lithium administration induces a significant increase in axon regeneration and functional recovery.

Lithium and the Phosphoinositide 3-Kinase/ Glycogen Synthase Kinase-3 Pathways

Clinically, the administration of lithium at physiological doses activates PI3K (Dong et al., 2014) while inhibiting GSK3 (Zhang et al., 2003). This is by phosphorylating GSK3α on its Ser 21 and Ser 9 sites (Hur and Zhou, 2010; Eldar-Finkelman and Martinez, 2011), the primary mechanism of GSK3 inactivation (Seira and Del Rio, 2014). This activation controls a host of cytoskeletal, microtubule, and microtubule-based motor- and the actin-based motor proteins that coordinate microtubule assembly at the growth cone leading to axon extension (Hur et al., 2011). While most of these proteins are GSK3 substrates, some contain conserved GSK3 sites. Thus, GSK3 is a major growth cone regulatory molecule by controlling local axon assembly and axon regeneration (Zhou and Snider, 2005; Hur et al., 2011).

Lithium-induced PI3K activity is the same as that activated by nerve injury. However, lithium can both promote and inhibit axon regeneration (Diekmann and Fischer, 2015). Although these are opposite outcomes, they are explained by the data coming from studies with significant differences. Among these are comparing the analysis of axon regeneration in the peripheral nervous system *vs*. the central nervous system, data from *in vitro* studies on different cell types derived from different animal models, and cells from animals of different ages (Eldar-Finkelman and Martinez, 2011; Wang et al., 2012). Other significant differences include comparing the effects of the same GSK3 inhibitors at different concentrations (Hur and Zhou, 2010; Eldar-Finkelman and Martinez, 2011), the effects of different GSK3 inhibitors (Eldar-Finkelman and Martinez, 2011; Beurel et al., 2015), which induce varying degrees of GSK3 inactivation (Kim et al., 2006; Hur and Zhou, 2010), drugs that act on one, the other, or both GSK3 isoforms (Eldar-Finkelman and Martinez, 2011; Beurel et al., 2015), and drugs that phosphorylate substrates at different molecular locations (Conde and Caceres, 2009; Eldar-Finkelman and Martinez, 2011). Therefore, GSK3 regulates the transcription of diverse genes, which affect both axonal transport and cytoskeletal dynamics, which, in turn, regulate axon regeneration. Each of these issues is discussed in greater detail by Diekmann and Fisher, 2015 (Diekmann and Fischer, 2015).

Following sciatic nerve injury, the inhibition of GSK3 in the neuron cell body increases the extent of axon regeneration and functional recovery (Gobrecht et al., 2014; Diekmann and Fischer, 2015; Huang et al., 2019). This is via the induction of the neuronal transcription-dependent axon regeneration program (Smad1), c-Jun, and cAMP response element-binding protein (CREB) (Saijilafu et al., 2013; Gobrecht et al., 2016). This, in turn, increases the extent of sciatic nerve axons and functional recovery (Diekmann and Fischer, 2015; Huang et al., 2019). Conversely, depleting Smad1 in adult mice prevents axon regeneration (Saijilafu et al., 2013).

Inhibiting GSK3 at the peripheral nerve growth cone also enhances the extent of axon regeneration (Conde and Caceres, 2009). Suppressing, but not blocking, GSK3 activity in growth cones by the local application of a GSK3 suppressor induces local cytoskeletal assembly, axon elongation (Saijilafu et al., 2013), and increased axon branching (Nagai et al., 2016). Thus, GSK3-mediated phosphorylation of microtubule-associated protein 1B reduces microtubule detyrosination, which resulting in axon regeneration by promoting the assembly of growth cone cytoskeletal microtubule-binding proteins and stabilizing growth cone microtubules (Gobrecht et al., 2014, 2016; Liz et al., 2014).

Physiologically, Schwann cell differentiation is induced by nerve injury-induced Schwann cell loss of axon contact and injury-activated PI3K and GSK3 inactivation. This differentiation involves changes in gene transcription, biochemistry, morphology (Qian et al., 2018; Wang et al., 2019; Zhang et al., 2019), proliferation, and the release of cell adhesion molecules and neurotrophic factors (Kim et al., 2000; Yang et al., 2008; Jessen and Mirsky, 2016; Wong et al., 2017; Jessen and Arthur-Farraj, 2019; Jessen and Mirsky, 2019). These Schwann cells phagocytize the degenerating axon and myelin sheath debris to clear the distal nerve pathway, which allows for axon regeneration (Napoli et al., 2012; Smith et al., 2013; Jessen and Mirsky, 2016; Clements et al., 2017; Cunningham et al., 2020).

Lithium participates in this process by inhibiting GSK-3, leading to increasing levels of Schwann cells β-catenin by preventing β-catenin degradation while also provoking β-catenin nuclear localization (Chen et al., 2016). This drives β-catenin to bind to T-cell factor/lymphoid-enhancer factor response elements in myelin genes leading to Schwann cell differentiation (Makoukji et al., 2012; Chen et al., 2016). Similarly, lithium induces Schwann cell proliferation, and their expression and release of cell adhesion molecules, and neurotrophic and other factors that promote further Schwann cell proliferation and axon myelination (Arthur-Farraj et al., 2012; Jessen and Mirsky, 2016; Gu et al., 2020). The enhanced proliferation is promoted by the Schwann cell intracellular signal transduction pathway, which increases their expression and phosphorylation of CREB (Grimes and Jope, 2001). Simultaneously, lithium suppresses Schwann cell migration by suppressing tau protein levels (Lei et al., 2017; Yi et al., 2019). Although lithium can inhibit Schwann cell proliferation and differentiation *in vitro* (Pinero et al., 2017), this action may be due to those studies involving the administration of lithium together with cAMP, or cAMP analogs, which alters lithium's influences on Schwann cells.

The administration of lithium at the time of a nerve crush suppresses GSK3. Simultaneously lithium induces Schwann cells to upregulate the remyelination transcription factors Oct6 and Sox10 (Makoukji et al., 2012; Fang et al., 2016), their expression of peripheral myelin-related genes, and levels of myelin protein zero and peripheral myelin protein 22 (Makoukji et al., 2012). Thus, the oral administration of lithium to mice at the time of a sciatic nerve injury leads to the almost complete elimination of myelin and axon debris after one week, while in control animals, phagocytosis is only just being initiated (Chen et al., 2016). Lithium also induces myelination (Ogata et al., 2004), while increasing the rate of axon myelination and myelin thickness (Chen et al., 2016; Fang et al., 2016). This directly increases the rate of axon regeneration and the extent

of functional recovery (Kidd et al., 2013; Chen et al., 2016; Ji et al., 2019).

Lithium and c-Jun Pathway

c-Jun is a regulator of the Schwann cell injury response and controls their gene expression, structure, and function related to their promotion of axon regeneration (Arthur-Farraj et al., 2012; Jessen and Mirsky, 2016). Both peripheral nerve injury (Hongisto et al., 2003; Arthur-Farraj et al., 2012) and lithium administration (De Felipe and Hunt, 1994; Shy et al., 1996) induce an immediate and massive Schwann cell expression of c-Jun. This leads to the cascade of changes discussed above, whereby Schwann cells promote axon regeneration and functional recovery (da Silva et al., 2014).

Nerve injury-induced c-Jun expression is required to prime neurons for axon outgrowth (Jenkins et al., 1993; Raivich et al., 2004). Thus, in mice, the administration of lithium and its induction of c-Jun following facial nerve injury increases the extent of axon regeneration (Herdegen et al., 1997; Raivich et al., 2004). Conversely, c-Jun knockdown in adult significantly reduces axon regeneration (Raivich et al., 2004; Saijilafu et al., 2011).

Nerve injury-induced elevation of c-Jun expression in peripheral sensory and motor neurons is long-lasting, and its level only decreases after the axons reinnervate their targets (de Felipe et al., 1993; Herdegen et al., 1993; Leah et al., 1993). This suggests that the loss of a target-derived factor underlies injury-induced c-Jun expression and that c-Jun remains expressed as long as that factor is not available (Kenney and Kocsis, 1998). A potential target-derived factor for dorsal root ganglion neurons is nerve growth factor (Gold et al., 1993). These data suggest that the on-going expression of lithium-induced c-Jun expression maintains axons in a regenerative state.

Lithium and Bcl-2

The protoncogene Bcl-2, which is present throughout the peripheral nervous system (Merry et al., 1994), is best known as an apoptosis-suppressor gene involved in inhibiting or inducing cell death (Hardwick and Soane, 2013). However, it also plays critical roles in cell physiology related to neuronal activity, autophagy, calcium handling, mitochondrial dynamics and energetics, and other processes of normal healthy cells. The extent of sciatic nerve axon regeneration in mice deficient in Bcl-2 is significantly reduced (Kotulska et al., 2005).

Bcl-2 stimulates axon regeneration by increasing intracellular Ca^{2+} signaling and activating both CREB and extracellular-regulated-kinase (Jiao et al., 2005). For injured neurons expressing Bcl-2, axotomy decreases endoplasmic reticulum Ca^{2+} uptake and storage and induces Ca^{2+} influx, which leads to a larger intracellular Ca^{2+} response than is seen in control neurons. Thus, Bcl-2 supports axon regeneration through the endoplasmic reticulum Ca^{2+} regulation (Jiao et al., 2005).

For cultured mouse retinal ganglion cells, the administration of lithium induces a large long-term increase in the Bcl-2 expression (Manji and Chen, 2002), which is associated with promoting neuron survival and inducing neurite outgrowth (Huang et al., 2003). Thus, lithium promotes axon regeneration by inducing Bcl-2 expression.

Lithium Induces Angiogenesis

Axons fail to regenerate across nerve gaps (> 5 cm in length) bridged with a sensory nerve graft because such long grafts fail to become vascularized (Sondell et al., 1999; Vargel, 2009; Hoben et al., 2015). Similarly, with increasing patient age, fewer axons regenerate across nerve grafts of increasing length due to an age-related decrease in nerve injury-induced angiogenesis (Gunin et al., 2014). However, axons successfully across longer nerve grafts in rats (Kanaya et al., 1992) and clinically (Doi et al., 1992), when the grafts are vascularized (Campodonico et al., 2020). The role of vascularization in promoting axon regeneration is seen by more extensive axon regeneration developing across nerve grafts treated with vascular endothelial growth factor (Pereira Lopes et al., 2011; Hoyng et al., 2014).

Lithium induces angiogenesis *in vivo* (Li et al., 2019; Liu et al., 2019) via activation of the Wnt/(beta)-catenin pathway (Zeilbeck et al., 2014). This suggests that lithium administration might increase sensory nerve graft vascularization leading to more extensive axon regeneration and functional recovery.

Lithium: Adverse Indications

The effects of lithium administration for treating depression have been well studied for more than 50 years (Gould et al., 2004). More recently, it has been studied for treatment of neurodegenerative disorders (Matsunaga et al., 2015; Raja et al., 2015; Moors et al., 2017), for its anti-inflammatory (Basselin et al., 2007), and anti-oxidant (Machado-Vieira et al., 2007; Jornada et al., 2011) effects, and its ability to promote angiogenesis (Liu et al., 2019) and axon regeneration (Fu et al., 2014; Su et al., 2014; Fang et al., 2016; Zhang et al., 2018b). However, there is little evidence for concern about adverse indications, especially for relatively short-termed lithium administration, as would be required for promoting peripheral axon regeneration and restoring function.

Conclusions

Lithium triggers almost all of the essential cellular and molecular mechanisms required to initiate and promote axon regeneration and enhance neurological recovery. At physiological doses, lithium induces axon regeneration in animal models and clinically (Zhang et al., 2003; Eldar-Finkelman and Martinez, 2011; Dong et al., 2014) while being free from adverse indications. Therefore, more extensive studies are required to determine whether the administration of lithium enhances the extent of axon regeneration and neurological recovery.

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