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Sesquiterpene lactones as potential drugs treating nerve injury

Philipp Gobrecht, Marco Leibinger, Dietmar Fischer*

Traumatic axonal lesions of peripheral nerves disrupt neuronal connections with their targets, resulting in the loss of motor and sensory functions. Despite the peripheral nervous system's capacity for axonal regrowth, this may lead to permanent impairements resulting in a loss of quality of life and a high socioeconomic burden. For example, peripheral nerve injuries in the upper extremities are relatively common, especially due to work-related accidents, and can lead to significant morbidity and long-term costs. A study found that 30% of patients with work-related nerve injuries experienced permanent disabilities, requiring financial compensation and impacting their quality of life. The estimated lifetime cost per patient with severe injury, including treatment, rehabilitation, and compensation, is approximately €102,167, highlighting the substantial economic impact of these injuries (Bergmeister et al., 2020). While these nerves have, in principle, the capacity to regenerate, the pace of recovery alongside age depends on the nature and severity of the injury. Additionally, the chance of functional recovery declines as the distance between the lesion and the target increases due to the relatively slow axonal growth rates, typically not exceeding 2–3 mm daily. Consequently, regrowth into the target tissue may require several weeks to months following traumatic nerve injuries in the extremities. This is problematic since the necessary regenerative support of Schwann cells diminishes over time, eventually leading to muscle atrophy in denervated areas (Sulaiman and Gordon, 2013). Moreover, the decreasing support of Schwann cells with time delays functional recovery and can even prevent axons from reaching their appropriate targets and, eventually, cause lifelong functional loss. Furthermore, regenerating axons frequently exhibit misguided growth, leading to neuromas around the injury site, culminating in chronic, arduous-to-treat pain. Therefore, the limited axonal growth rate can significantly compromise patients' life quality and is associated with substantial socioeconomic costs and prolonged professional downtimes (Bergmeister et al., 2020). Despite substantial research efforts over the last decades, therapies and interventions aiming to accelerate axon growth and thus improve functional recovery have lacked efficiency in the clinic or were unsuitable because of severe side effects. For example, several preclinical studies have explored neurotrophic factors, such as nerve growth factor and brain-derived neurotrophic factor, to enhance axonal regeneration (Zheng et al., 2016). These factors play crucial roles in the survival and growth of neurons, and their exogenous application has demonstrated positive effects on nerve repair in preclinical models (Faroni et al., 2015). However, the use of neurotrophic factors in humans is limited by significant challenges such as short half-life, inefficient delivery methods, and potential side effects. Another promising pharmacological strategy for enhancing axon regrowth following nerve damage is the utilization of tacrolimus. This immunosuppressive drug has been shown to support axonal growth in preclinical studies and clinical case reports. The exact mechanisms underlying its neuroregenerative effects are not fully understood. Still, these positive effects on regenerating nerve fibers are separate from its immunosuppressive actions and primarily target the injured neuron (Daeschler et al., 2023). However, the systemic use of the drug is limited by significant side effects such as nephrotoxicity and immunosuppression. Therefore, drugs that promote axon regeneration with acceptable side effects are still unavailable in the clinic, highlighting the urgent need for further research and innovation. The discovery that constitutively active glycogen synthase kinase 3 (GSK3) significantly speeds up axon regeneration in peripheral nerves and understanding the underlying mechanism has opened up novel possibilities for pharmacological approaches (Gobrecht et al., 2014). GSK3 is a serine/threonine kinase with two isoforms encoded by separate genes, GSK3α and GSK3β. Studies involving knockin mice that express constitutively active forms of GSK3 ($GSK3^{S/A}$) have demonstrated markedly accelerated axon regeneration in the injured sciatic nerve and functional recovery in adult mice (Gobrecht et al., 2014). This effect on axon growth results from GSK3's influence on microtubule dynamics within the growing axons. The underlying mechanism involves the kinase's ability to phosphorylate microtubule-associated protein 1 B (MAP1B), which reduces the microtubule detyrosination level - a post-translational modification known to reduce microtubule dynamics in axon growth cones and thus limits the axonal growth rate (**Figure 1**; Gobrecht et al., 2024a). Microtubule detyrosination in neurons is controlled by different enzymatic actions that add or remove the C-terminal tyrosine residue of tubulin. Tubulin tyrosine ligase adds a tyrosine residue to the detyrosinated α-subunit of tubulin dimers before they are added to microtubule plus-ends, thus restoring the tyrosinated state at the C-terminal end (**Figure 1**). There is no evidence of interaction between phosphorylated MAP1B (pMAP1B) and tubulin tyrosine ligase. Instead, pMAP1B reduces microtubule detyrosination by binding to tyrosinated microtubules and hindering the access of detyrosinating enzymes (Barnat et al., 2016). These enzymes removing tyrosine, also known as carboxypeptidases, were identified as vasohibin-1 (VASH1) and vasohibin-2 (VASH2) (Aillaud et al., 2017). The small vasohibin-binding protein (SVBP) is an essential cofactor for the activity of vasohibin enzymes, implying a tightly regulated enzymatic collaboration that ensures precise control over microtubule dynamics within neurons. A partial knockdown of vasohibin enzymes (VASH1 or VASH2) or SVBP slightly shifts the balance of detyrosinated to tyrosinated microtubules to an extent as similarly found in regenerating axonal

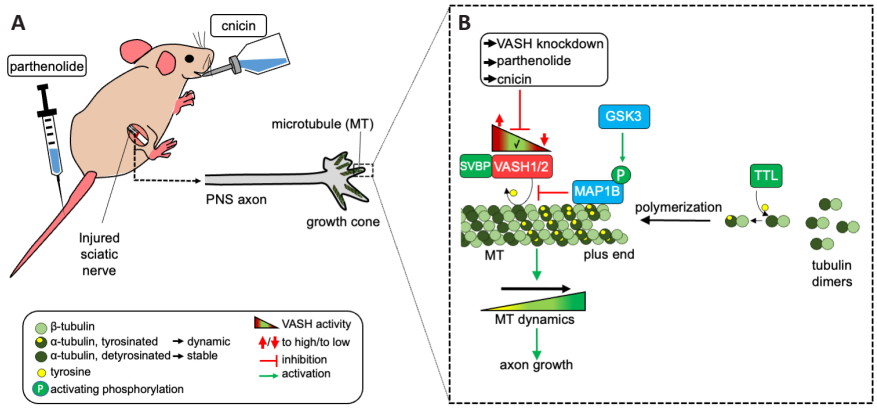

Figure 1 | **Optimized α-tubulin detyrosination levels accelerate axon growth.**
(A) Parthenolide and cnicin promote axon regeneration following sciatic nerve injury by modulating microtubule (MT) dynamics in axonal growth cones. In contrast to parthenolide, which requires injection, cnicin allows oral application due to its high bioavailability. (B) MTs elongate by polymerizing tubulin dimers at the tubules plus ends. Tubulin dimers with detyrosinated α-tubulin attach more frequently to the plus end while forming less stable MTs. Vasohibins 1 and 2 (VASH1/2) and the small vasohibin-binding protein (SVBP) as a cofactor remove the tyrosine residues of α-tubulin, while the tubulin tyrosine ligase (TTL) restores its tyrosinated state. Glycogen synthase kinase 3 (GSK3) activates microtubule-associated protein 1B (MAP1B) via phosphorylation, hindering MT detyrosination. Like MAP1B activity, partial VASH knockdown or pharmacological inhibition via parthenolide or cnicin reduces MT detyrosination, enhancing MT dynamics and accelerating axon growth. To achieve axon growth-promoting effects, VASH inhibition needs to be balanced. Excessive inhibition by complete knockdown or very high parthenolide/cnicin concentrations has adverse effects. Created with Microsoft PowerPoint.

growth cones of postnatal neurons (Gobrecht et al., 2024a), which typically show higher growth rates. Consistently, axon growth speed of adult neurons was also accelerated to similar levels as in the postnatal state (Gobrecht et al. 2024a). Consistently, the axonal growth rate of adult neurons increases to similar levels as postnatal neurons in culture (Gobrecht et al. 2024a). However, a complete knockdown of each enzyme alone already shifts the balance of detyrosinated and tyrosinated microtubules to suboptimal levels, which have either no beneficial, or even adverse effects on axon growth, underscoring the delicate equilibrium required to achieve optimal microtubule dynamics and axon growth (Gobrecht et al., 2024a). The finding that partial vasohibin knockdown promotes axon regeneration led to investigating whether a pharmacological intervention can mimic these effects. The sesquiterpene lactone parthenolide, a naturally occurring compound of the plant Tanacetum parthenium, was identified as an inhibitor of vasohibins, impacting the detyrosination-tyrosination balance of microtubules (Li et al., 2019). We have shown in various studies that parthenolide promotes axon growth of cultured dorsal root ganglion neurons from adult rats and mice and even primary retinal ganglion cells derived from rodent and human tissue (Leibinger et al., 2023; Gobrecht et al., 2024a). Moreover, *in vivo* experiments in different rodent models of peripheral nerve injury also demonstrated the great potential of parthenolide as daily repeated intravenous injections of 2 µg/kg markedly reduced the recovery time of motor and sensory function after sciatic nerve injury and accelerated the growth of motor, sensory, and sympathetic axons in the nerve (Gobrecht et al., 2024a). Parthenolide remained effective even when the treatment started a couple of days after the nerve injury. Despite its promising preclinical results in speeding up axon regeneration, parthenolide faces a significant hurdle in its low oral bioavailability, which limits its administration to parenteral routes. As repeated daily doses showed the most robust results, there is a considerable limitation regarding costs and treatment adherence. Another sesquiterpene lactone, cnicin, a natural compound found in blessed thistle (cnicus benedictus), promotes axon regeneration in various species, likely also by inhibiting VASHs (Gobrecht et al., 2024b). However, compared to parthenolide, cnicin has two advantages over parthenolide in terms of potential therapeutic agents for nerve regeneration. Firstly, cnicin exhibits an oral bioavailability of 84.7% in rats. Secondly, it lacks the potentially mutagenic and allergenic epoxy group found in parthenolide, making it a potentially safer alternative and a strong candidate for further drug development (Gobrecht et al., 2024b). Cnicin promoted axon growth in rodent neuronal cultures and, as parthenolide, even in cultured adult primary human neurons (Gobrecht et al., 2024b). Moreover, it demonstrated efficacy in rats, mice, and rabbits at 2 µg/kg daily doses. Even intravenous administration of cnicin at 4 mg/kg (2000-fold higher than the effective oral dose) for 2 weeks did not result in observable toxicity or body weight changes in rats, suggesting a favorable safety profile for human treatment.

Thus, while preclinical studies have demonstrated the great potential of parthenolide in promoting axon regeneration, its therapeutic translation is hampered by its poor oral bioavailability. In contrast, cnicin, with its favorable pharmacokinetic profile, high oral bioavailability, absence of a potentially mutagenic epoxy group, and demonstrated efficacy in promoting axon regeneration across multiple species, emerges as an even more promising candidate for further development. However, rigorous clinical trials are essential to ascertain its safety and efficacy in humans, determine optimal dosages, and evaluate its therapeutic potential across various nerve injury types and clinical settings. The identification of sesquiterpene lactones as a promising therapeutic might be a significant advancement toward developing effective treatments for nerve damage, offering hope for improved outcomes and enhanced quality of life of patients.

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Philipp Gobrecht, Marco Leibinger, Dietmar Fischer*
Center of Pharmacology, Institute for Pharmacology, Medical Faculty and University of Cologne, Cologne, Germany
***Correspondence to:** Dietmar Fischer, PhD, dietmar.fischer@uni-koeln.de.
https://orcid.org/0000-0002-1816-3014 (Dietmar Fischer)
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倍半萜内酯作为治疗神经损伤的潜在药物
文章特色分析

一、文章重要性

1. 临床需求迫切：

外周神经损伤常见且治疗困难，功能恢复缓慢，导致患者长期残疾和社会经济负担。目前缺乏有效促进神经再生的药物。

2. 机制研究深入：

文章从分子机制（GSK3－MAP1B－微管去酪氨酸化）出发，揭示了调控轴突再生速度的关键通路，为药物开发提供了明确靶点。

3. 转化潜力显著：

提出了两种具有明确作用机制的天然产物衍生物，尤其是 cnicin，具备高口服生物利用度和良好安全性，具备直接推向临床研究的潜力。

二、创新性特色

1. 靶点新颖：

首次将 vasohibins/SVBP 微管去酪氨酸化酶系统作为促进轴突再生的药物靶点，并验证其部分抑制可模拟发育期神经的高生长速率。

2. 药物再定位：

将已知天然产物 parthenolide 和 cnicin 重新定位为 vasohibin 抑制剂，拓展了其临床应用前景。

3. 多物种验证：

在啮齿类、兔类及人源神经元中均验证了药物的有效性，增强了结果的普适性与临床转化价值。

4. 药代动力学优势：

Cnicin 具备 84.7%的口服生物利用度，且无 parthenolide 的致突变性环氧基团，更适用于长期治疗。

三、对学科的启示

1. 神经再生药物开发的新方向：

表明通过调控微管后翻译修饰（如去酪氨酸化）可有效促进成年神经元的轴突再生，为神经修复提供了新策略。

2. 天然产物的药物化潜力：

强调天然产物在神经再生药物筛选中的重要性，尤其是结构优化后可提升其成药性。

3. 转化研究的典范：

从基础机制（GSK3－MAP1B－VASH）到药物发现（parthenolide/cnicin），再到多物种 preclinical 验证，构建了完整的转化研究链条。

4. 临床治疗策略的拓展：

提示未来神经损伤治疗可能不再局限于手术修复或神经营养因子，小分子口服药物有望成为辅助或主导治疗手段。

总结

本文不仅在机制层面深化了对轴突再生调控的理解，更在转化医学层面提出了具有高成药性的候选药物，尤其是 cnicin，具备进入临床前和临床试验的潜力。该研究为神经再生领域的药物开发提供了新靶点、新策略与新希望，对神经科学、药理学和康复医学均具有深远影响。