Parthenolide: a novel pharmacological approach to promote nerve regeneration

Traumatic axonal lesions disrupt the connections between neurons and their targets, leading to loss of motoric and sensory functions. Although lesioned peripheral nerves can principally regenerate, the rate of recovery depends on the mode and severity of the respective injury (Grinsell and Keating, 2014). While injuries close to the innervation site have good chances of recovery, long distance regeneration is particularly problematic due to relatively slow axonal growth rates, which even under favorable conditions do not normally exceed 1–2 mm per day (Sunderland, 1947).

For this reason, re-growth into the respective target tissue can take several months or even years after nerve injuries in arms and legs. Within months, however, the regenerative support of Schwann cells declines and denervated muscles atrophy. Under these conditions, re-innervation of appropriate targets and consequently functional recovery are at least impaired if not impossible. Moreover, regenerating axons are often misguided and form so-called neuromas around the injury site, causing chronic, difficult-to-treat pain. Despite a high capacity for axonal regrowth in the peripheral nervous system, nerve injuries therefore often seriously impair the quality of life of affected patients and are overall associated with high socio-economic costs and long professional downtimes (Lad et al., 2010).

In spite of substantial research efforts, therapies for nerve injuries have not considerably changed over the last 30 years and clinical outcomes often remain unsatisfactory. The treatment of primary axonal traumatata generally depends on the severity of the injury (Grinsell and Keating, 2014; Tung, 2015). Slight nerve contusions are normally left untreated to heal spontaneously, while severed nerves need surgical intervention to re-adapt the two ends. Gaps can be bridged with autologous nerve transplants, which unfavorably require sacrifice of healthy nerves. Removal of, for example, the sural or the antebrachial cutaneous nerve then leads to collateral numbness in the outside of the foot and inside of the arm, respectively. Alternatively, synthetic nerve guides can be implanted into short lesion sites, but these enable so far only insufficient nerve regeneration (Grinsell and Keating, 2014).

All in all, surgical interventions performed to re-adapt severed nerves cannot sufficiently solve the problem of slow and often incomplete functional recovery. For these reasons, approaches aiming at accelerating axonal re-growth in order to shorten recovery times and to minimize secondary tissue changes are nowadays considered paramount.

Particularly important for the re-growth of severed axons and the survival of injured neurons are neurotrophic factors such as nerve growth factor (NGF) or brain-derived neurotrophic factor (BDNF). Their respective expression/secretion is, however, reduced upon prolonged regeneration, which is why application of exogenous neurotrophic factors accelerates and promotes axonal regeneration in animal models (Grinsell and Keating, 2014; Faroni et al., 2015). Unfortunately, this approach proofed so far largely inapplicable to clinical therapeutics to speed up axonal growth, as their administration is difficult and provokes serious side effects in humans (Grinsell and Keating, 2014). Likewise, use of chemicals such as 4-methylcatechol, which stimulate the production of endogenous NGF and BDNF, is expected to cause similar toxicity and is so far not approved for clinical use. Neurotrophic activity has also been ascribed to the immunosuppressor FK506 (Tacrolimus). Enhanced axonal regeneration upon autologous nerve transplantation was contributed to immunosuppression as well as potentiation of endogenous NGF (Grinsell and Keating, 2014). However, prolonged and systemic administration of FK506 to support tedious nerve regeneration is associated with high risks of infection, bone fractures and hypertension as a result of its drastic immunosuppressive side effects (Tung, 2015).

Hormones might be used alternatively or complementary to growth factors for the treatment of nerve injuries. Thyroid and growth hormones improved re-myelination of regenerated axons in experimental animal models, while neuroactive steroids such as progesterone positively affect Schwann cell physiology and nerve regeneration. Accordingly, TSPO (18 kDa translocator protein) ligands such as 4-choleodiazepam (RO5-4864) and etifoxine (Stresam®), which stimulate the generation of endogenous neuroactive steroids, may promote regenerative axon growth (Faroni et al., 2015). Although etifoxine is approved in some countries for anxiety disorders, it can potentially induce severe side effects such as hepatitis and has not yet been clinically used for nerve repair. Severed axons themselves have been shown to be amenable to direct, polyethylene glycol-mediated fusion (Grinsell and Keating, 2014), but functional recovery after this treatment is still lengthy and incomplete. Furthermore, coordination of initial axon outgrowth was improved upon short electrical stimulation of transected nerves, which reduced functional recovery time upon traumatic nerve injury (Tung, 2015). The efficacy of these novel therapeutic approaches in human patients is currently investigated in two separate clinical trials. They are, however, only applicable after surgical intervention directly at the site of a traumatic nerve transection, but not for wider-spread crush injuries or generalized multifocal peripheral neuropathies.

Our recent studies demonstrated that genetically modified mice with constitutively active glycogen synthase kinase 3 (GSK3) recover significantly faster from sciatic nerve crush than respective wildtype animals (Gobrecht et al., 2014, 2016; Diekmann and Fischer, 2015). In these mutant mice, motor and sensory skills almost completely recovered by 14 days after injury, while controls reached only about 50% at this time point. Additional experiments indicated that elevated GSK3 activity increased MAP1B phosphorylation and inhibited the detyrosination of microtubules in axonal growth cones, leading to increased axonal growth in culture (Gobrecht et al., 2014). This effect was mimicked by parthenolide (PTL), a sesquiterpene lactone that naturally occurs in the plant feverfew (Tanacetum parthenium). PTL reduced microtubule detyrosination in axonal tips of cultured dorsal...
regeneration at very low concentrations and independent of NF-κB (Gobrecht et al., 2016), we do not expect any serious side effects even for long-term applications. Therefore, we consider PTL and DMAPT attractive candidates for further validation as therapeutic for traumatic nerve injuries, potentially representing a milestone in the promotion of nerve regeneration. Furthermore, it seems feasible that they might also prove beneficial for disease- and drug-induced multifocal axonal damages as part of generalized neuropathies, which considerably constrain the quality of life of more and more affected patients.

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References


