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Treatment of Diabetic Neuropathy with Nitric Oxide Gel

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Abstract

Our study investigates a novel therapy to address a vascular factor that contributes to the development of diabetic peripheral neuropathy (DPN) using five experimental groups of a mouse model that spontaneously develops diabetes. The compound under investigation is a nitric oxide (NO)-donating topical gel which has potential as a treatment for preventing and treating DPN.

Background

It is estimated that 74% of diabetic patients suffer from DPN. These patients report sensations of burning, shooting, and lancinating pain, allodynia, paresthesia, hyperesthesia, aching, cramping, or tingling. Most treatments, such as analgesics, antidepressants, and anticonvulsants, only address symptoms of DPN. These treatments have proven useful for pain management but do not address the underlying causes of DPN.

It is hypothesized that there are both vascular and neural components in the development of neuropathy in addition to an oxidative damage component. We hypothesize that by addressing the vascular component of the neuropathy, the pathological cellular environment that contributes to the development and progression of neuropathy can be mitigated, and a healthy cellular environment will encourage recovery of nerve function, in addition to promoting the health of surrounding tissues, tending toward reduction of diabetic ulcers and prevention of amputations in human patients.

Nitric oxide is synthesized endogenously in the endothelium from L-arginine, oxygen, and NADPH by endothelial nitric oxide synthase (eNOS). Normally, nitric oxide diffuses into smooth muscle cells. There, it activates guanylate cyclase, increasing cytoplasmic concentrations of cyclic guanosine monophosphate, which in turn binds to regulatory subunits of Protein Kinase G, activating it and facilitating phosphorylation of multiple proteins, notably myosin. Myosin filaments then relax and elicit vasodilation.

Experimental Design

We aim to introduce exogenous nitric oxide into the vascular system of neuropathic limbs via a topical gel that will be applied on a daily basis in order to elicit vasodilatory effects similar to those produced by endogenous NO, thereby promoting normal perfusion and nerve function.

The experiment will use a mouse model genetically predisposed to spontaneously develop diabetes, and thus diabetic neuropathy, BKS.Cg db/db, and a non-diabetic, wild-type control, BKS.Cg wt/wt.

This study will utilize five experimental groups:
1. Non-diabetic control - Provides histology and nerve data of healthy, non-diabetic BKS mouse

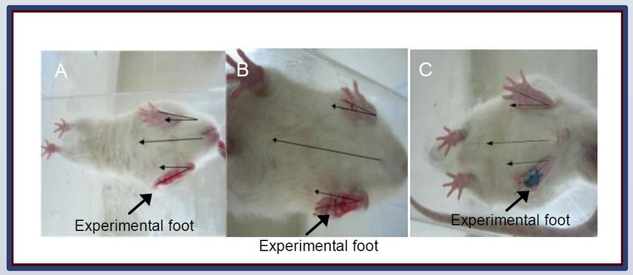
2. Diabetic sham with inactive gel - Treated with an inactive gel in order to control for potential effects on the vasculature arising from manual application of topical gel

3. Diabetic preventative - Treated with the gel from the beginning of the experiment to observe the effects of the NO gel in preventing DPN

4. Diabetic rescue - Treated with the gel only after onset of DPN in order to assess the efficacy of NO in reversing developed DPN

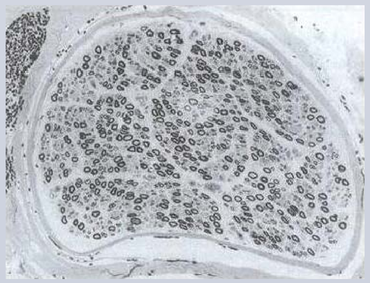
5. NO Dosing group - Used to determine an appropriate dose of NO for the BKS model

Mice will be tested to monitor loss of motor control and sensation caused by DPN, and the recovery of control and sensation which we hypothesize will occur as a result of treatment with the NO-donating gel. Sensory nerve function will be determined with the use of a Von Frey Dynamic Plantar Aesthesiometer, while motor nerve function will be determined by footprinting.

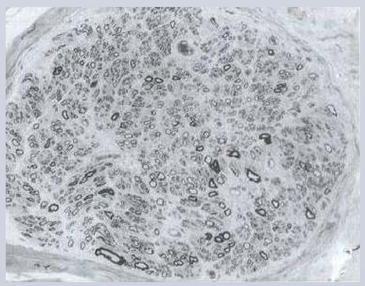


Motor: Measuring Toe Spread with footprinting

Sensory: Dynamic Plantar Aesthesiometer



Healthy nerve



Neuropathic nerve

Nerve histology will be performed on a regular basis in order to visually ascertain nerve condition and regeneration.

Expected Outcomes

Due to the ability of NO to promote vasodilation, providing needed nutrients to the nerves, it is expected that the animals in groups three and four will show improved nerve function when compared to the diabetic mice who do not receive the treatment, thus demonstrating the efficacy of this gel as a treatment for DPN.

References

1. Tessari P, Cecchet D, Cosma A, et al. Nitric Oxide Synthesis Is Reduced in Subjects With Type 2 Diabetes and Nephropathy. *Diabetes.* 2010;59(9):2152-2159.

2. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care.* 2006;29(7):1518-1522.

3. Rassaf, T, Preik, M, Kleinbongard, P, et al. Evidence for in vivo transport of bioactive nitric oxide in human plasma. *Journal of Clinical Investigation J Clin Invest.* 2002;109(9):1241-1248

4. Shabani M, Pulfer SK, Bulgrin JP, Smith DJ. Enhancement of wound repair with a topically applied nitric oxide-releasing polymer. *Wound repair and regeneration : official publication of the Wound Healing Society [and] the European Tissue Repair Society.* 1996;4(3):353-362.

5. Sullivan KA, Hayes JM, Wiggin TD, et al. Mouse models of diabetic neuropathy. *Neurobiol Dis.* 2007;28(3):276-285.

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