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Corneal Confocal Microscopy: Bedside-to-Bench

Aim: To assess the biomarker potential of corneal nerves in experimental diabetic neuropathy.
Methods: Streptozotocin-induced diabetic mice were used for the experiments. The following drugs were used for the treatment of diabetic neuropathy: ciliary neurotrophic factor (CNTF); the glucagon-like peptide 1 (GLP-1) analog exendin-4; cyclopentolate; glycopyrrolate; and gallamine. CNFT, exendin-4, or vehicle were applied daily as a single 50 µL drop to one eye for the last 2 weeks of diabetes. Cyclopentolate or vehicle were applied daily as a single 50 µL drop to one eye for the last 4 weeks of diabetes. Glycopyrrolate, gallamine or vehicle were delivered daily by sub-cutaneous injection for 12 weeks from diabetes onset. Corneal confocal microscopy (CCM) was used to estimate corneal nerve density in the subbasal nerve plexus and stroma. Peripheral neuropathy was also assessed by means of peroneal motor nerve conduction velocity (MNCV), paw heat and tactile sensation.
Results: CCM was performed in control and diabetic mice at baseline, 8 and 12 weeks (study end). At study end, vehicle-treated diabetic mice had significantly reduced corneal nerve density compared to vehicle-treated control mice and diabetic mice treated daily with either topical CNTF or exendin-4. By contrast, corneal nerve density of diabetic mice treated with either CNTF or exendin-4 recovered to control level. At study end, diabetic mice treated with topical cyclopentolate showed comparable corneal nerve density to vehicle-treated control mice. Furthermore, cyclopentolate alleviated small fiber-mediated paw heat hypoalgesia and large fiber-MNCV slowing in a dose-dependent manner. By contrast, vehicle-treated diabetic mice showed markedly reduced corneal nerve density. Finally, systemic glycopyrrolate for 12 weeks, but not gallamine, prevented corneal nerve loss, paw heat hypoalgesia and MNCV slowing compared to vehicle-treated diabetic mice. Across all experiments, corneal nerve reduction was limited to the subbasal nerve plexus level with intact stroma suggestive of a distal dying-back neuropathy.
Conclusions: These results underpin the utility of CCM as a biomarker for in-vivo efficacy studies of novel neuroprotective treatments that are initially identified by in-vitro assays.

Comments. Diabetic animals and rodents are essential components of the drug development process due to common features with human neuropathy such as NCV slowing, loss of heat sensation and sensory nerves in the epidermis. However, as in humans, invasive biopsy is not suitable for longitudinal studies in the same animal. The present study shows efficacy of CNTF, exendin-4, and cyclopentolate in preventing or restoring diabetes-related corneal nerve loss in diabetic mice. Delivery of cyclopentolate to the eye also improved functional measures of large and small fiber neuropathy. Furthermore, glycopyrrolate prevented both onset of the same functional deficits and corneal nerve loss. Thus, corneal nerve assessment by CCM may add value in assessing the efficacy of novel therapeutics in animal models of neuropathy.

Ioannis N. Petropoulos

Reference. Jolivalt CG, Han MM, Nguyen A, Desmond F, Alves Jesus CH, Vasconselos DC, Pedneault A, Sandlin N, Dunne-Cerami S, Frizzi KE, Calcutt NA. Using Corneal Confocal Microscopy to Identify Therapeutic Agents for Diabetic Neuropathy. J Clin Med. 2022 Apr 21;11(9):2307. doi: 10.3390/jcm11092307.
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