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Topical Delivery of Muscarinic Receptor Antagonists Prevents and Reverses Indices of Neuropathy in Mouse Models of Type 1 and Type 2 Diabetes

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Sensory neurons express muscarinic type 1 receptors (M1R) and M1R agonism constrains neuronal growth via suppression of mitochondrial function. Systemic delivery of M1R antagonists prevented and reversed peripheral neuropathy in rodent models of type 1 and type 2 diabetes. We extended exploration of the therapeutic potential of M1R antagonists by determining efficacy following topical delivery. STZ-diabetic mice developed paw thermal hypoalgesia and loss of intra-epidermal nerve fibers. Topical delivery of the selective M1R antagonist pirenzepine (30 min/day for 8-12 weeks in hydrogel) to the paw significantly prevented these indices of neuropathy at concentrations of 2-10%, but not in the 0.2-1% dose range. Withdrawal of treatment resulted in gradual progression to thermal hypoalgesia over 4-8 weeks. Established thermal hypoalgesia in the db/db mouse model of type 2 diabetes was gradually reversed over 4 weeks following instigation of daily topical delivery of the muscarinic antagonists pirenzepine or oxybutynin (30 min of 2% drug in hydrogel). Topical delivery of the non-selective muscarinic antagonist atropine (30 min of 2% drug in hydrogel) to STZ-diabetic mice also prevented paw thermal hypoalgesia and loss of IENF. Moreover, daily topical delivery of atropine (20µl of 2% in saline) to the eye prevented loss of sub-basal nerves of the cornea in STZ-diabetic mice, as measured by corneal confocal microscopy. No effect was seen in the contralateral untreated eye. Reduced corneal nerve density in STZ-diabetic mice was reversed within 2 weeks by daily treatment with the specific M1R antagonist MT7 (30µl of 25ng/ml in saline). These data show local efficacy of diverse M1R antagonists against functional and structural indices of sensory neuropathy when applied to the skin or eye. The current medicinal use of topical M1R antagonists for other conditions suggest that rapid translation of these findings to clinical studies is viable.

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