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A novel curcumin derivative for the treatment of diabetic neuropathy

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ABSTRACT

Neuropathy is a common complication of long-term diabetes. Proposed mechanisms of neuronal damage caused by diabetes that are downstream of hyperglycemia and/or loss of insulin signaling include ischemic hypoxia, inflammation and loss of neurotrophic support. The curcumin derivative J147 is a potent neurogenic and neuroprotective drug candidate initially developed for the treatment of neurodegenerative conditions associated with aging that impacts many pathways implicated in the pathogenesis of diabetic neuropathy. Here, we demonstrate efficacy of J147 in ameliorating multiple indices of neuropathy in the streptozotocin-induced mouse model of type 1 diabetes. Diabetes was determined by blood glucose, HbA1c, and insulin levels and efficacy of J147 by behavioral, physiologic, biochemical, proteomic, and transcriptomic assays. Biological efficacy of systemic J147 treatment was confirmed by its capacity to decrease TNFα pathway activation and several other markers of neuroinflammation in the CNS. Chronic oral treatment with J147 protected the sciatic nerve from progressive diabetes-induced slowing of large myelinated fiber conduction velocity while single doses of J147 rapidly and transiently reversed established touch-evoked allodynia. Conduction slowing and allodynia are clinically relevant markers of early diabetic neuropathy and neuropathic pain, respectively. RNA expression profiling suggests that one of the pathways by which J147 imparts its protection against diabetic induced neuropathy may be through activation of the AMP kinase pathway. The diverse biological and therapeutic effects of J147 suggest it as an alternative to the polypharmaceutical approaches required to treat the multiple pathogenic mechanisms that contribute to diabetic neuropathy.

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1. Introduction

Diabetic neuropathy disrupts the quality of life of over half of all people with type 1 and type 2 diabetes. There is no FDA-approved treatment for diabetic neuropathy and the only current recommendation for prevention and slowing of symptoms is the maintenance of glycemic control (Pop-Busui and Martin, 2016). Unfortunately, maintaining consistent euglycemia is difficult for the majority of people suffering from diabetes. Preclinical studies have suggested that the pathogenesis of diabetic neuropathy may derive from both hyperglycemia and loss of neurotrophic support from insulin/C-peptide. Multiple downstream pathways have been identified, which creates both opportunity and challenges for developing therapies (Biessels et al., 2014; Yagihashi, 2016; Zochodne, 2016). The traditional approach has been to target one pathway to establish proof of concept and then demonstrate clinical efficacy. However, there is emerging recognition that polypharmacy may be required in order to target multiple pathogenic pathways (Davidson et al., 2015). It would therefore be most beneficial to develop a therapy that impacts multiple pathways that contribute to diabetic neuropathy. To accomplish this, we have investigated the curcumin derivative J147.

Curcumin is a polyphenol and the active component of turmeric and ginger. These spices have a long history of use in traditional medicine and the use of curcumin as a therapeutic has been investigated in multiple clinical studies against many diseases (Ara et al., 2016). Curcumin has anti-inflammatory, anti-oxidant, and neuroprotective properties, which are all potential contributors to the pathogenesis of diabetic neuropathy (Calcutt et al., 2009). Previous studies have shown that curcumin is effective in treating hyperalgesia, large fiber conduction slowing and central nervous system dysfunction in rodent models of diabetes (Ho et al., 2016; Joshi et al., 2013; Peeyush Kumar et al., 2011; Sharma et al., 2007), making curcumin a plausible therapeutic candidate for diabetic neuropathy. Unfortunately, curcumin demonstrates poor

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bioavailability and blood brain barrier permeability. To overcome this, we have developed the curcumin derivative J147 using a medicinal chemistry strategy employing cell based phenotypic screening assays based upon aging-associated brain toxicities (Chen et al., 2011). J147 is effective in preventing oxidative stress, reduced mitochondrial function, and nerve cell death due to the loss of trophic support in cell culture models. J147 reverses cognitive impairment in a mouse model of Alzheimer's disease, and enhances memory in both transgenic AD mice, and aged wild type mice. It also reduces inflammation and old age-associated metabolic decline in a mouse model of aging (Currais et al., 2015; Prior et al., 2013) and is neurogenic (Prior et al., 2016). The wide-ranging effects of J147 suggest that it has a strong therapeutic potential to reduce the multiple pathogenic pathways associated with diabetic neuropathy. We have therefore used the STZ induced model of type 1 diabetes in mice to explore the therapeutic effects of J147.

2. Materials and methods

2.1. Protocol

Female Swiss Webster mice were made diabetic by injection of STZ (90 mg/kg intraperitoneal in 0.9% sterile saline) on two consecutive days, with each injection preceded by a 12 h fast, as described in detail elsewhere (Jolivalt et al., 2016). Only animals with blood glucose levels of >15 mM at the start and end of the study were retained as diabetic. HbA1c was measured using the A1CNow kit (Bayer Healthcare, Toronto, Ontario, Canada). Insulin was measured using the ultra-sensitive mouse Insulin ELISA kit. (Crystal Chem). J147 was administered in corn oil vehicle by oral gavage via a gavage needle twice daily starting immediately after confirmation of diabetes.

2.2. Paw thermal sensitivity

Hind paw thermal response was measured as described in detail elsewhere (Jolivalt et al., 2016). Briefly, mice were placed in glass cubicles on top of a modified Hargreaves device (UARD, La Jolla, CA, USA), set at a heating rate of 1 °C/s to selectively activate C fibers (Yeomans and Proudfit, 1996). The heat source was placed directly below the middle of one of the hind paws and the time until paw withdrawal measured. To account for drift in heating rates over time, the apparatus was calibrated daily by constructing a time:-temperature response curve with temperature measured at the lower surface of the glass platform using an inbuilt thermistor. Response latency was converted to response temperature each day by interpolation from the calibration curve (Jolivalt et al., 2016).

2.3. Motor nerve conduction velocity

Motor nerve conduction velocity (MNCV) was measured in mice anesthetized with isoflurane using needle electrodes to stimulate (0.05 ms, 1–5 V) the sciatic nerve at the sciatic notch and Achilles tendon. Evoked electromyograms were recorded using needle electrodes placed in the ipsilateral interosseus muscles and MNCV calculated using the peak-peak latency between pairs of M or H waves and the distance between the two stimulation sites (Jolivalt et al., 2016). Nerve and rectal temperatures were maintained at 37 °C and all measurements were made in triplicate, with the median of the three used to represent values for that animal.

2.4. Paw tactile response threshold

Tactile allodynia was assessed using von Frey filaments as described in detail elsewhere (Jolivalt et al., 2016). Briefly, a series of filaments with a range of buckling forces were sequentially applied to the plantar surface of the mouse hindpaw following the up and down method of Dixon (1980). Data are represented as 50% paw withdrawal threshold (PWT).

2.5. Rotarod

Mice were placed on an accelerating rotarod device (4.0–40.0 rpm in 120 s) and time before falling recorded as described elsewhere (Jolivalt et al., 2016).

2.6. RNA analysis

RNA was isolated from whole brain using the Qiagen RNeasy Plus Universal mini kit (Qiagen). RNA-Seq libraries were prepared using the Illumina TruSeq Stranded mRNA Sample Prep Kit according to the manufacturer's instructions. Gene expression that were differentially expressed between the groups were analyzed using the Ingenuity Pathway Analysis software. (Qiagen).

2.7. Western blots

Tissue samples were homogenized in 10 vol of RIPA lysis buffer (50 mm Tris, pH 7.5, 150 mm NaCl, 0.1% sodium dodecyl sulfate, 0.5% deoxycholate, and 1% NP40) containing a cocktail of protease and phosphatase inhibitors. Samples were sonicated (2×10 s) and centrifuged at 10,000*g* for 60 min at 4 °C. Protein concentrations in the cell extracts were determined using the BCA protein assay (Pierce, Rockford, IL, USA). For SDS-PAGE, 20 μg of protein was used. Plasma samples were added directly to sample buffer. All samples were separated using 10 or 12% Criterion XT Precast Bis-Tris Gels (Bio-Rad, Hercules, CA, USA). Proteins were transferred to nitrocellulose membranes. Membranes were blocked with 5% skim milk in TBS-T (20 mm Tris buffer pH 7.5, 0.5 m NaCl, 0.1% Tween 20) for 1 h at room temperature and incubated overnight at 4 °C in the primary antibody diluted in 5% BSA in TBS/0.05% Tween 20. Primary antibodies used were: TNFα (CST), TSPO (Abcam), iNOS (BD Biosciences), GFAP (Millipore), Actin (CST), total AMPK (CST), phospho-AMPK (CST), and CRP (Sigma-Aldrich). Subsequently, blots were washed in TBS/0.05% Tween 20 and incubated for 1 h at room temperature in horseradish peroxidase-goat anti-rabbit or goat anti-mouse (Bio-Rad) diluted 1/5000 in 5% skim milk in TBS/0.1% Tween 20. After additional washing, protein bands were detected by chemiluminescence using the SuperSignal West Pico Substrate (Pierce). For all antibodies, the same membrane was re-probed for actin except for CRP where amido black was used. Autoradiographs were scanned using a Bio-Rad GS800 scanner. Band density was measured using the manufacturer's software. Proteins were normalized to actin or albumin band density. Phosphoprotein levels were normalized to total protein expression.

2.8. Statistical analyses

Statistical analysis was carried out by one-way ANOVA followed by Tukey-Kramer multiple comparison *post hoc* test. For data that incorporated multiple time points, two-way repeated-measures ANOVA and *post hoc* Tukey corrected t tests were applied. GraphPad Prism 6 was used to perform statistical analyses. All data are represented as group mean ± SEM.

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