

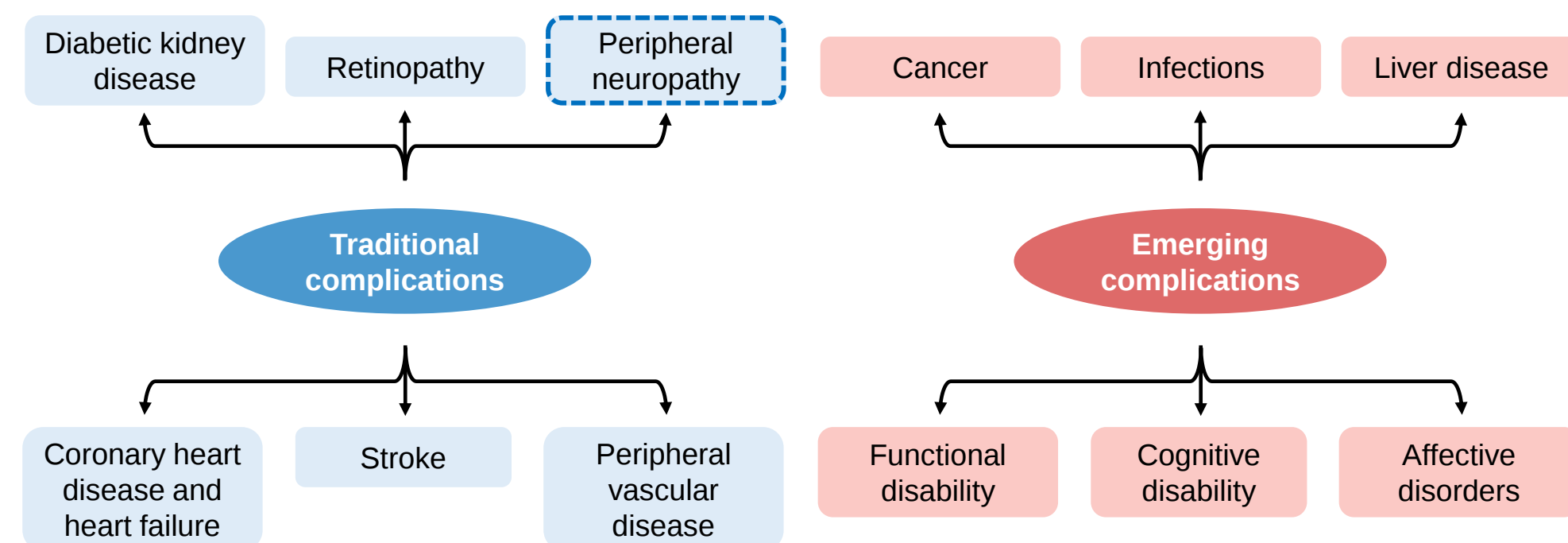
Establishment and Validation of Rodent Models for Diabetic Neuropathy: A Robust Platform for Therapeutic Evaluation

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Introduction

Diabetic neuropathy, which affects about 50% of diabetic patients, leads to chronic pain, sensory loss, increased risks of foot ulcers and amputations, significantly impacts quality of life and healthcare costs. Robust animal models are essential for research and therapeutic development, despite the challenges in replicating human pathophysiology and ensuring reproducibility. In this study, we developed diabetic neuropathy models using db/db mice and STZ-induced diabetic animals and completed efficacy testing on multiple agents to evaluate their therapeutic potential.



Methods & Experimental Design

Establishment of Models:

Diabetic neuropathy models were established using male db/db mice and STZ-induced Type 1 diabetic rats (single STZ injection, 65 mg/kg). Gabapentin (100 mg/kg for mice, 50 mg/kg for rats) was administered orally one hour before testing. Evaluations included paw withdrawal threshold (Von Frey test), sciatic nerve conduction velocity, intra-epidermal nerve fiber quantification (PGP9.5), and CGRP immunostaining.

Measurements in Mice and Rat Sciatic Nerves:

Animals were anesthetized. The sciatic notch and knee were stimulated with electrodes which were connected to a stimulator. The simultaneous electromyographies were recorded from the dorsum of the foot by two sterilized electrodes with an Amplifier. Motor nerve conduction velocity (MNCV) was calculated by dividing the distance between stimulating electrodes by the average latency difference between the peaks of the compound muscle action potentials evoked from 2 sites (sciatic notch and ankle). Sensory nerve conduction velocity (SNCV) was calculated by dividing the distance between stimulating and recording electrodes by the latency of the signal from the stimulation artifact to the onset of the peak signal. The distance was determined by stretching the foot so that a linear distance could be measured between stimulating and recording electrodes.

Readouts:

Sciatic-tibial MNCV, ankle-foot SNCV, sciatic-foot SNCV

Results

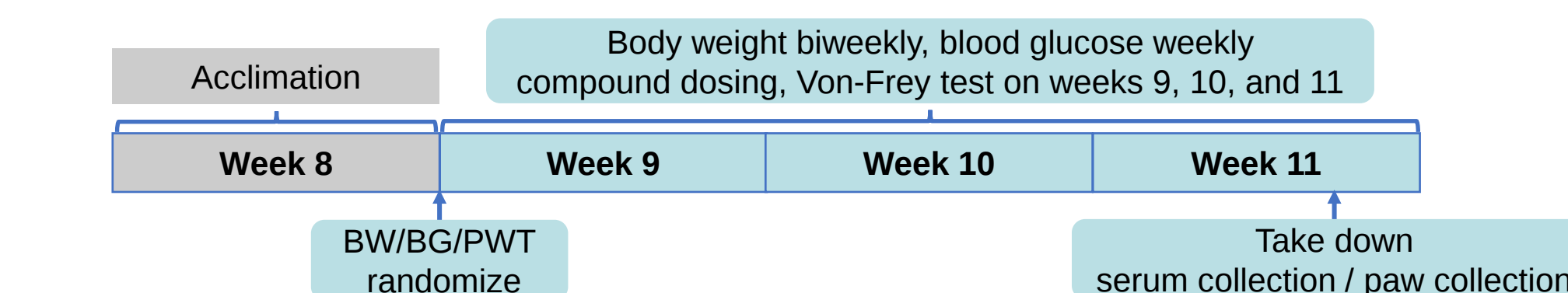


Figure 1. Experimental procedure of diabetic neuropathy in male db/db mice.

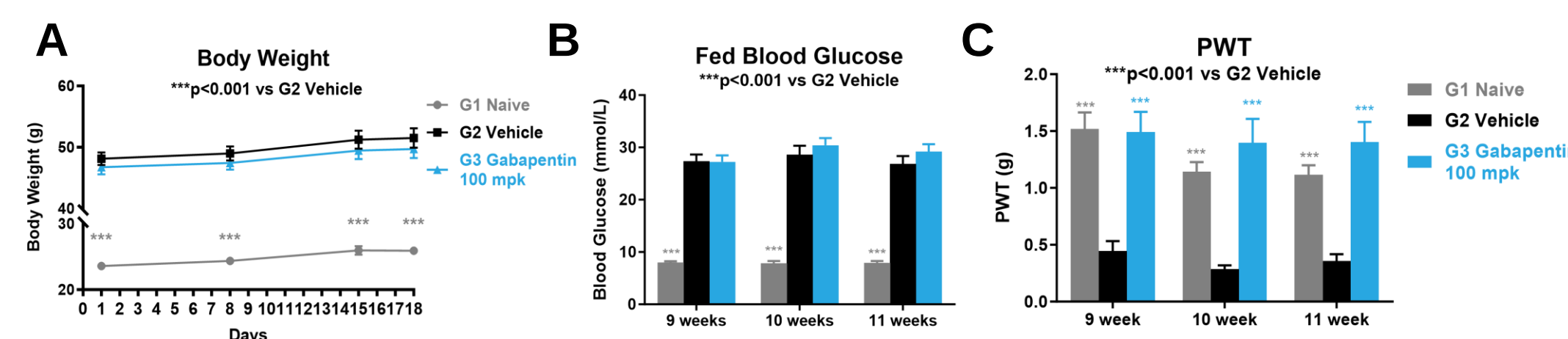


Figure 2. Effect of gabapentin (100 mpk) on A) body weight, B) fed blood glucose & C) pain withdrawal threshold (PWT) in diabetic neuropathic db/db mice, compared to naïve and untreated mice. Data are presented as mean±SEM, n=10/group, and analyzed by two-way ANOVA (A) or one-way ANOVA (B & C), followed by Dunnett's multiple comparison tests.

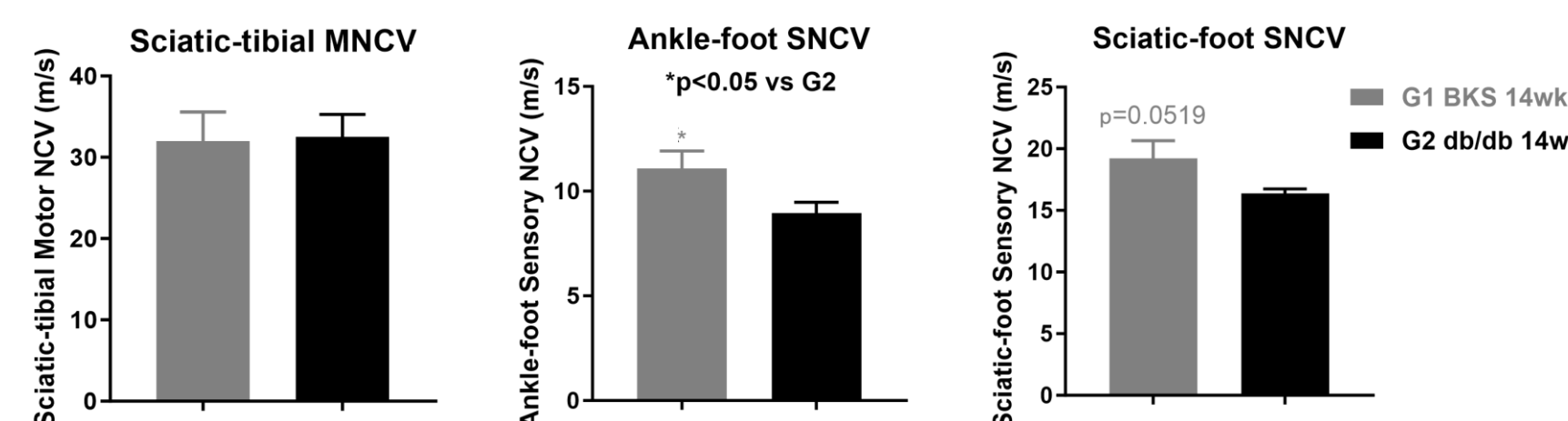


Figure 3. Nerve conduction velocity measurements in naïve (BKS) and peripheral diabetic neuropathic db/db mice. Data are presented as mean±SEM, n=5 for G1, n=6 for G2, and analyzed by Mann-Whitney tests.

Summary

Our study successfully established models of diabetic neuropathy, demonstrating significant neuropathic pain and impaired nerve conduction. Positive control treatments, including Pregabalin (30 mpk, 10 mpk, 5 mpk, p.o.), Gabapentin (50 mpk, p.o.), Naproxen (30 mpk, p.o.), SB-705498 (30 mpk, p.o.), Meloxicam (1 mpk, p.o.), Rimegepant (10 mpk, p.o.), Sumatriptan (1 mpk, p.o.), Carbamazepine (20 mpk, p.o.), effectively alleviated these complications, highlighting their potential therapeutic benefits.

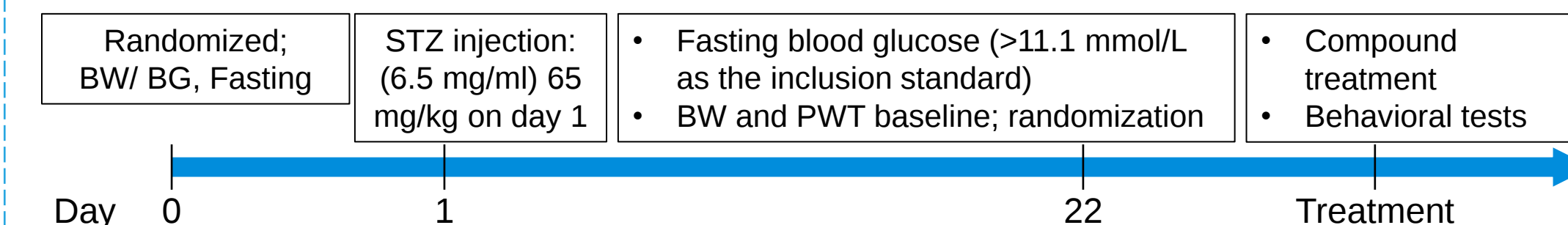


Figure 4. Experimental procedure of STZ-induced diabetic pain in 7-week-old male Sprague-Dawley rats.

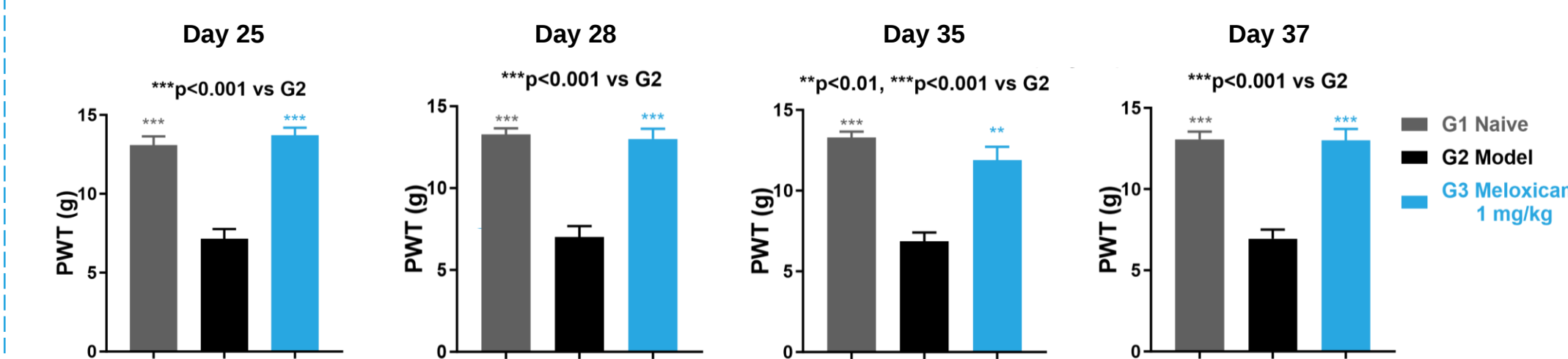


Figure 5. Effect of gabapentin (50 mpk), naproxen (30 mpk), SB-705498 (30 mpk) & meloxicam (1 mpk) on the paw withdrawal threshold (PWT) of diabetic neuropathic Sprague-Dawley rats, compared to naïve and untreated rats. Data are presented as mean±SEM, n=12/group, and analyzed by Kruskal-Wallis tests, followed by Dunn's multiple comparison tests.

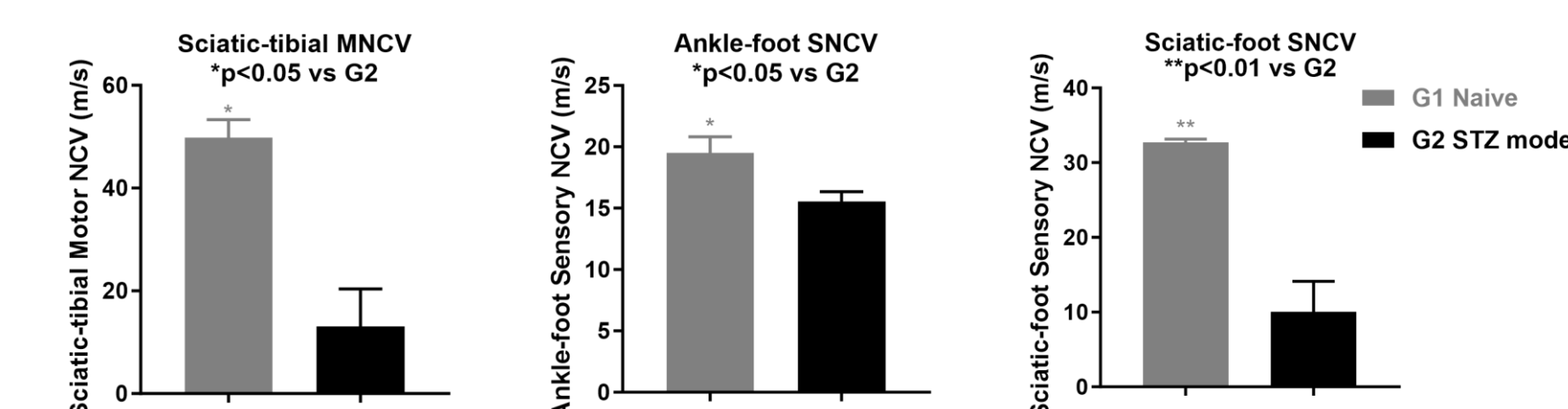


Figure 6. Nerve conduction velocity measurements in naïve and peripheral diabetic neuropathic Sprague-Dawley rats. Data are presented as mean±SEM, n=5 for G1, n=6 for G2, and analyzed by Mann-Whitney tests.

References

1. Tomic, D., Shaw, J.E. & Magliano, D.J. *Nat Rev Endocrinol* 18, 525–539 (2022).



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