AMDCC Neuropathy Core March 2006

Eva L. Feldman, M.D., Ph.D
Department of Neurology
JDRF Center
University of Michigan

AMDCC
THE ANIMAL MODELS OF DIABETIC COMPLICATIONS CONSORTIUM

AMDCC Definition of Neuropathy

- Evidence of clinical loss of sensory function
  - Tail flick and hind paw withdrawal latencies (TF and HP)
- Electrophysiological evidence of nerve impairment
  - Sensory and motor distal latencies and nerve conduction velocity (NCV)
- Anatomical evidence of nerve fiber loss
  - Intraepidermal fiber density (IEFD

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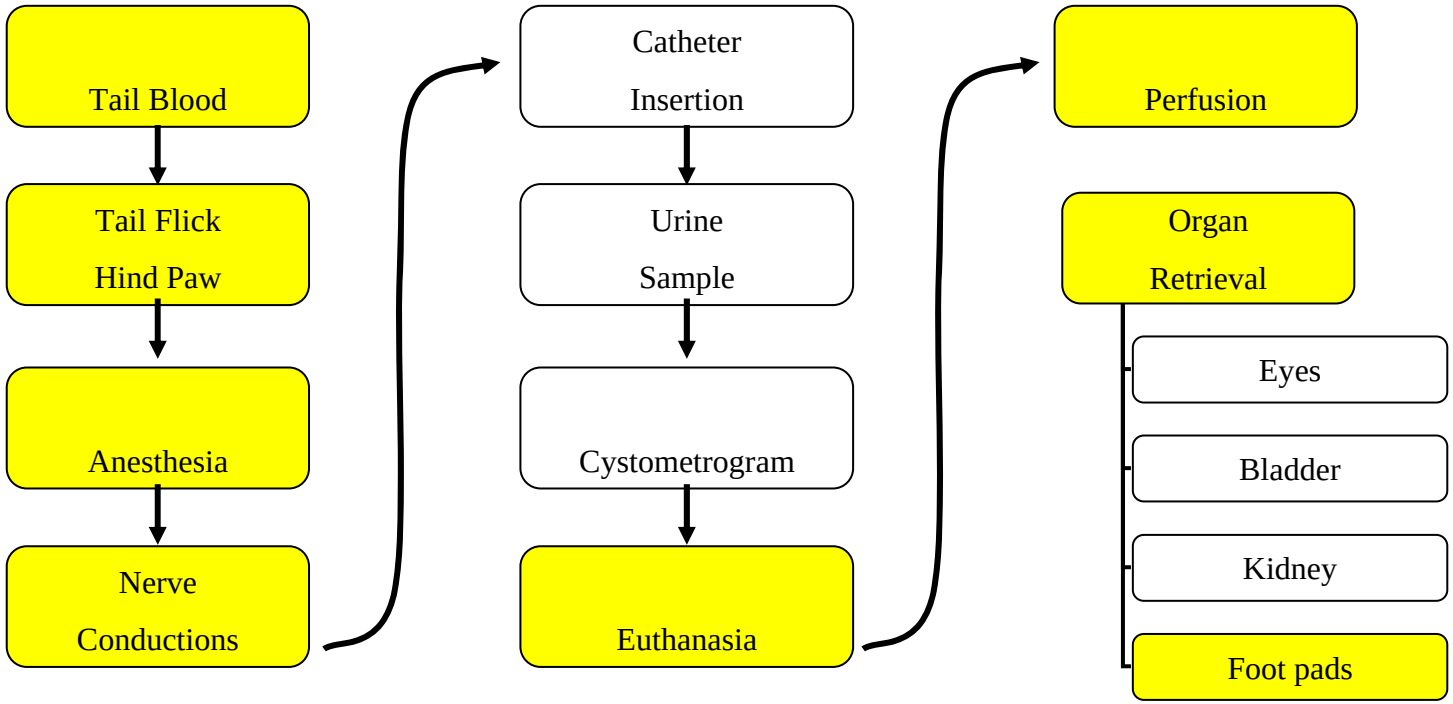
AMDCC Core Protocol



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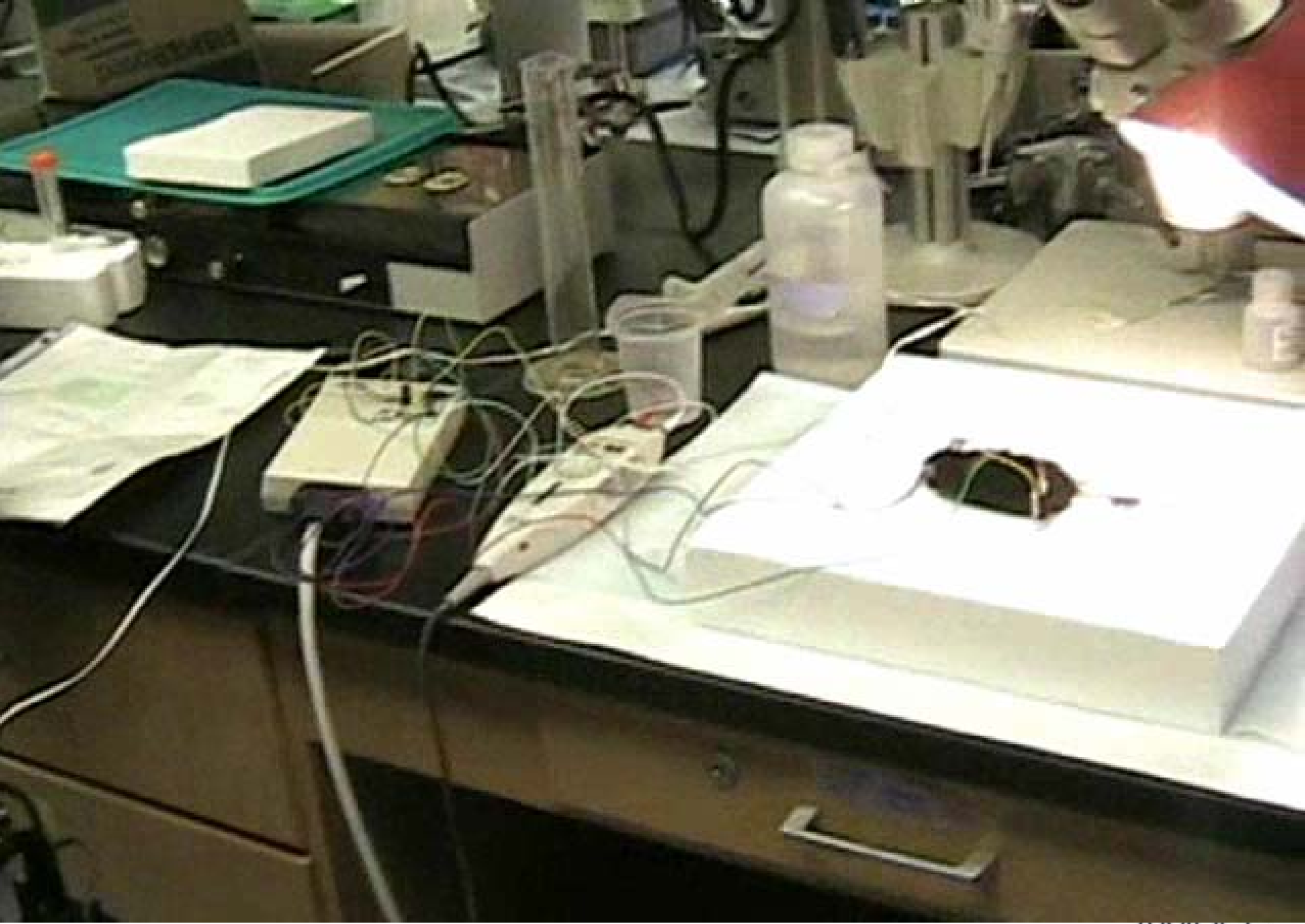
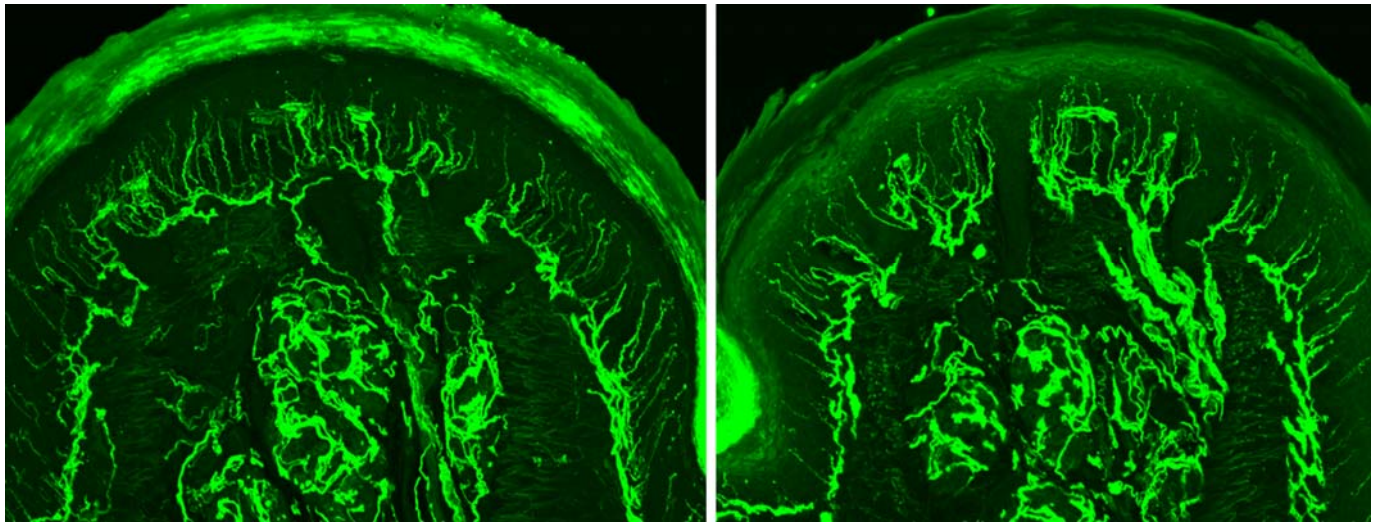
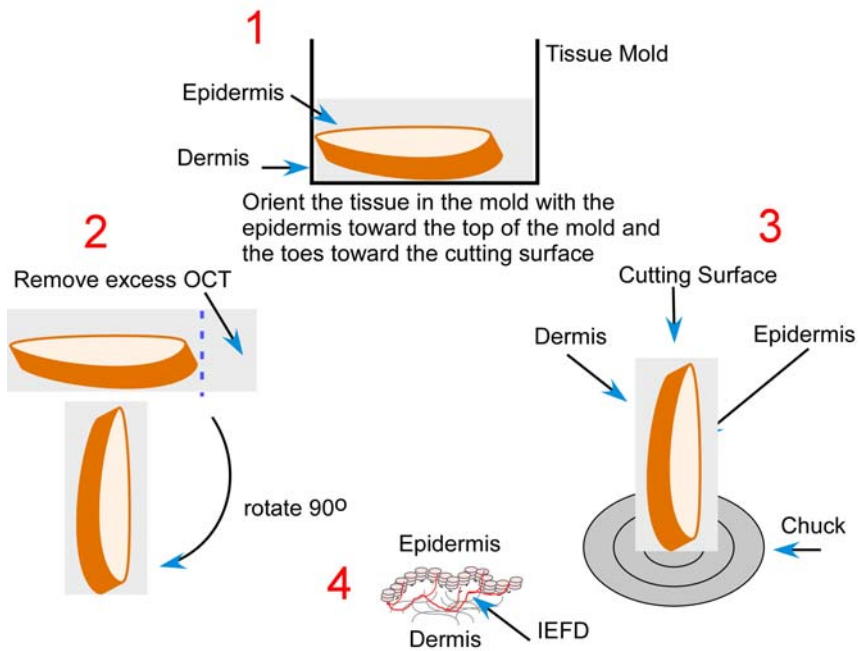
END



Intraepidermal Nerve Fiber Density





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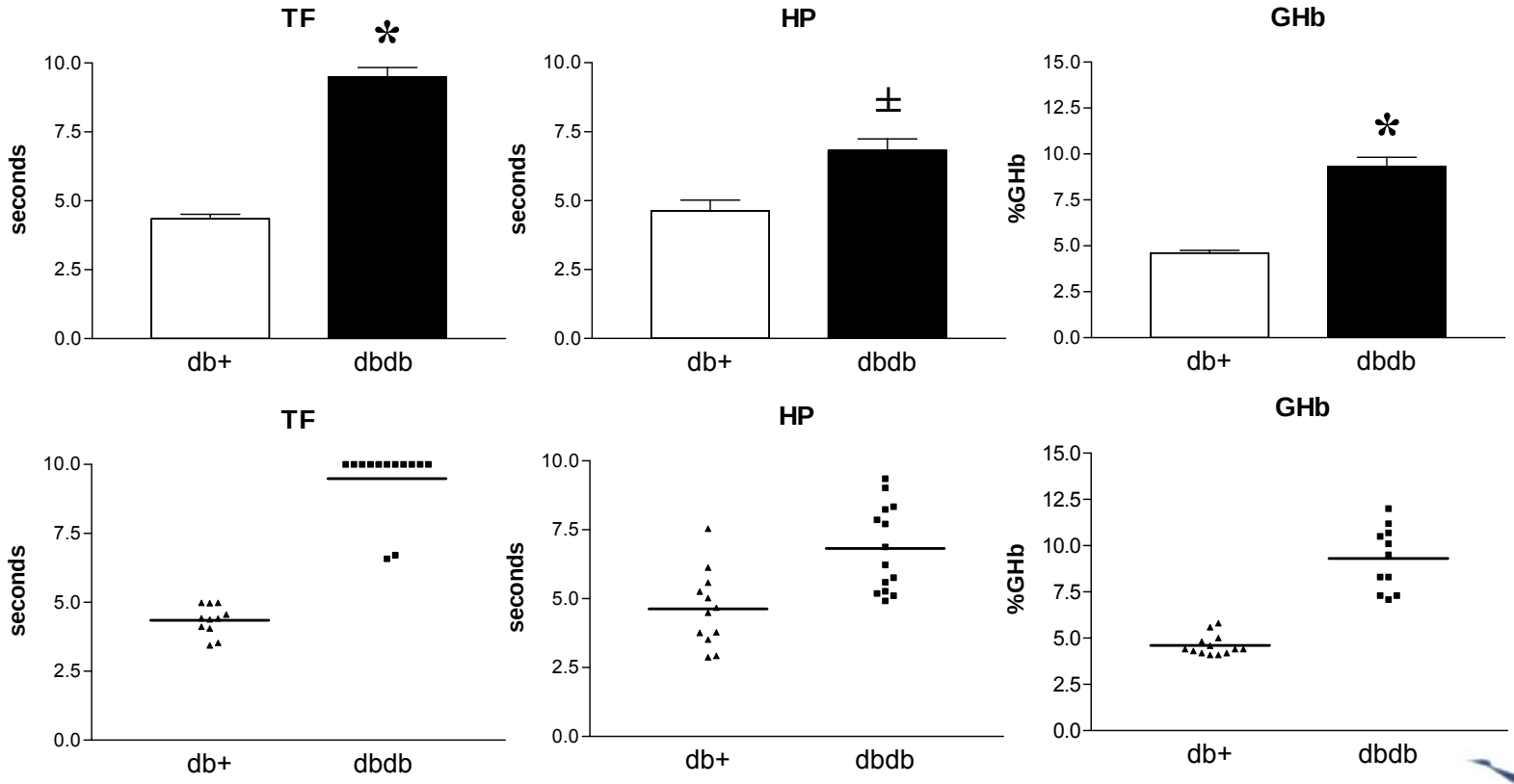
Sensory Tests
C57BLKS db/db Mice



*** P < .0001, ± P < .001**

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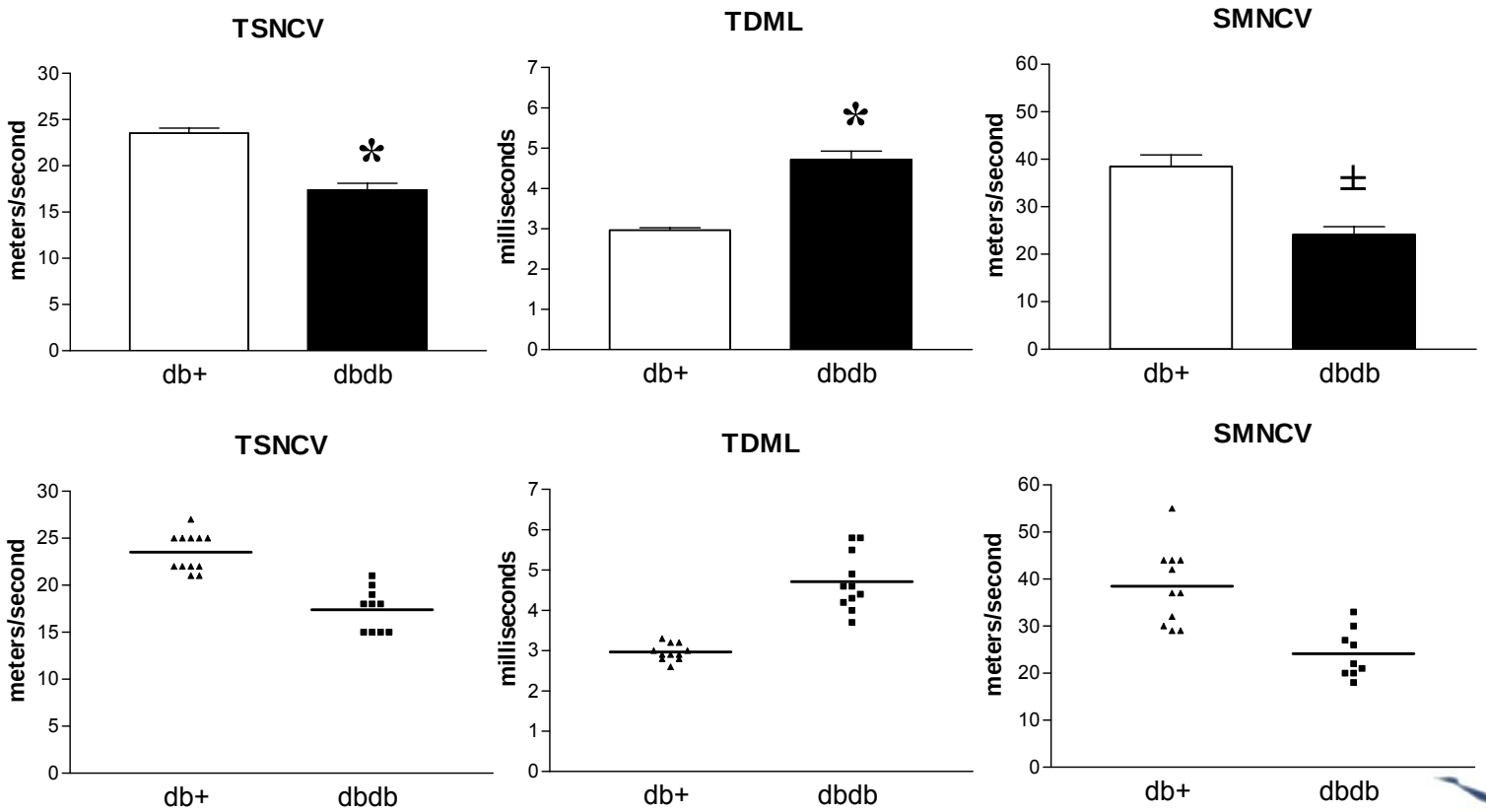
Nerve Conduction Velocity C57BLKS db/db Mice



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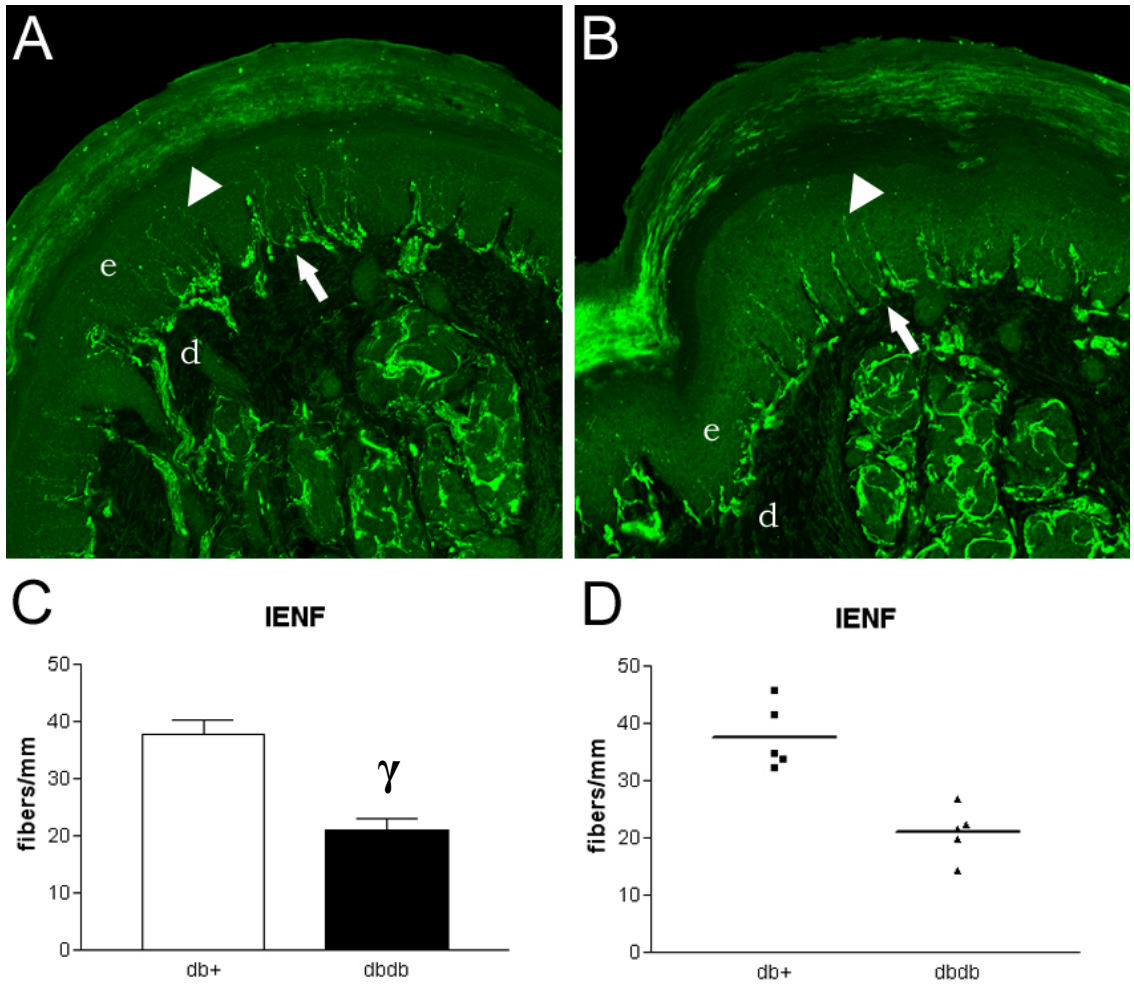
IENF Density
C57BLKS db/db Mice



γ P < .05

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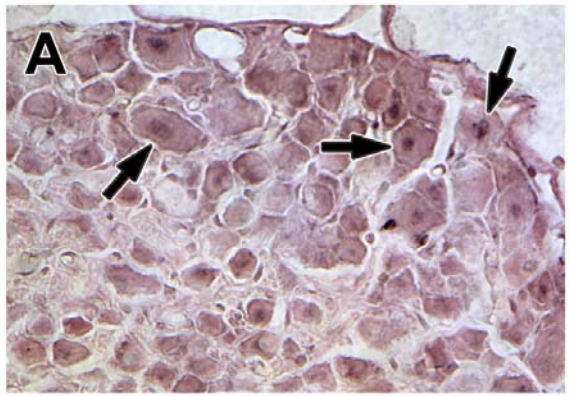
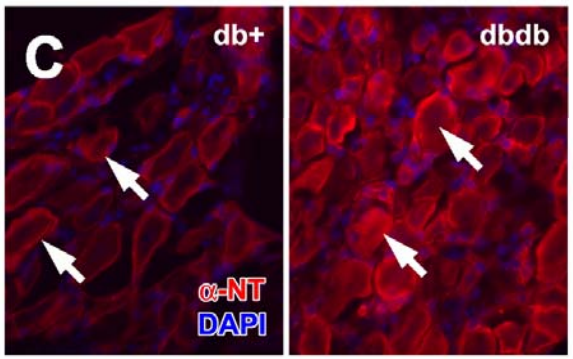
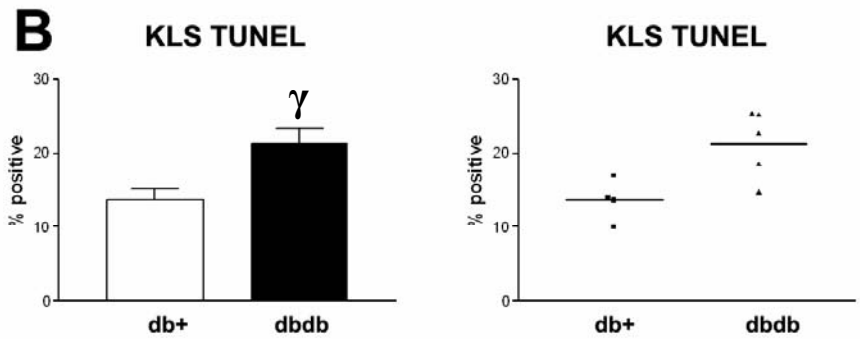
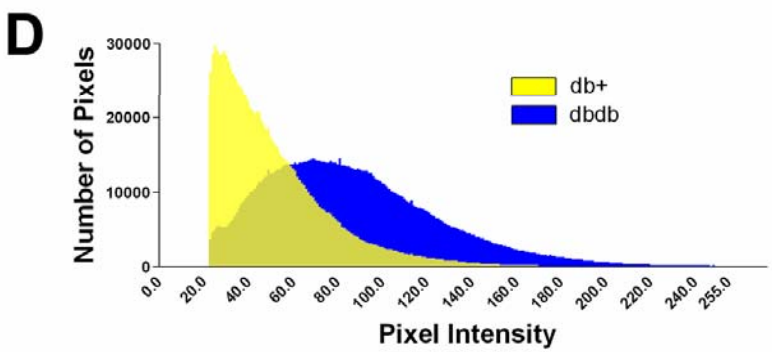
Neuropathy Advanced Phenotyping: TUNEL and Nitrotyrosine IHC









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Animal Models: Ongoing Phenotyping*

	Tail Flick Hind Paw every 8-12 weeks	**NCV Measured 12 or 16 and/or 24 weeks post-diabetes**	**IEFD Measured at tissue harvest**	**Biochemistry Measured at tissue harvest**	**Advanced Neuropathy Phenotyping**
C57BLKS db/db	X	X	X	X	X
C57BLKS db/db ± resveratrol	X	X	NA	X	NA
GCLC +/- db/db high fat diet	X	Ongoing	Ongoing	Ongoing	NA
GLUT1 tg db/db High fat diet	X	X	Ongoing	Ongoing	Ongoing
Nestin Cre// SOD2 loxP/loxP	X	X	X	X	Ongoing
Akita STZ	X	X	Ongoing	Ongoing	Ongoing
Pdx +/+ and +/-	NA	X	X	X	X
RAGE Tg STZ	Ongoing	Ongoing	Ongoing	Ongoing	Ongoing
DbA STZ ± rosiglitazone	Ongoing (only 12 wk)	Ongoing (only 12 wk)	Ongoing	Ongoing	Ongoing

X = completed NA = not applicable
*** Have phenotyped over 450 mice since 2002**

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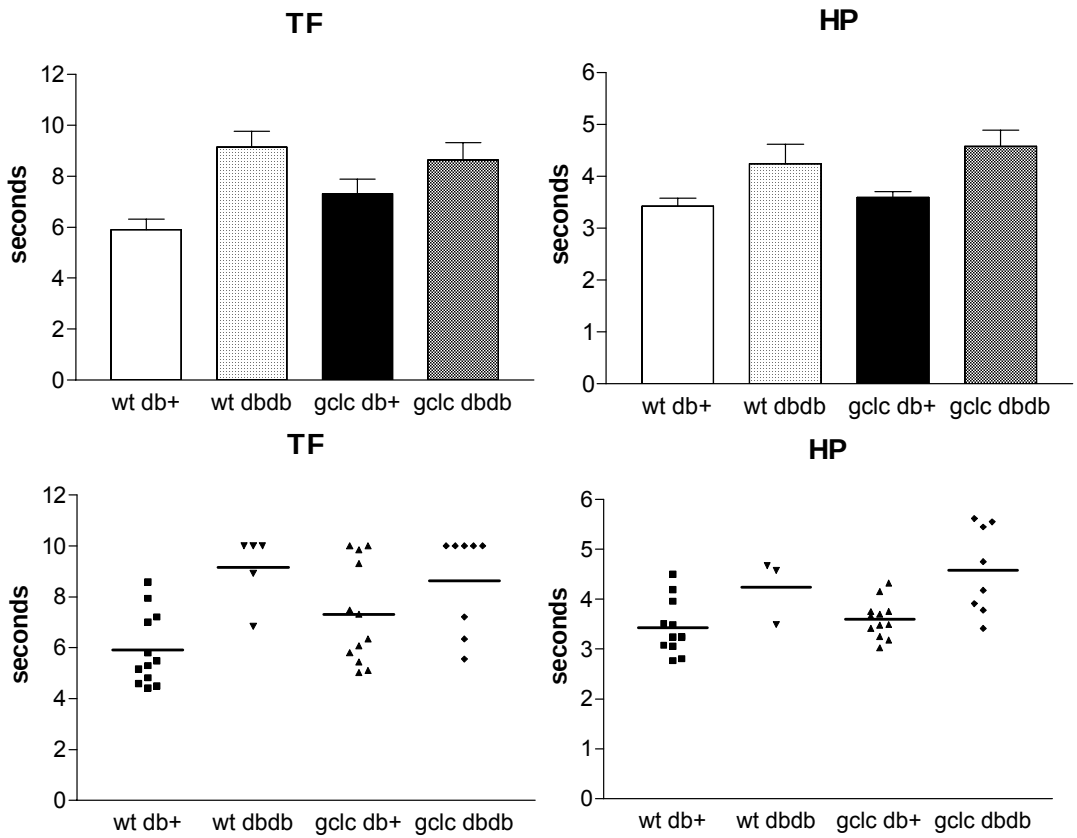
Sensory Tests
GCLC +/- db/db High Fat Mice



No Significant Differences

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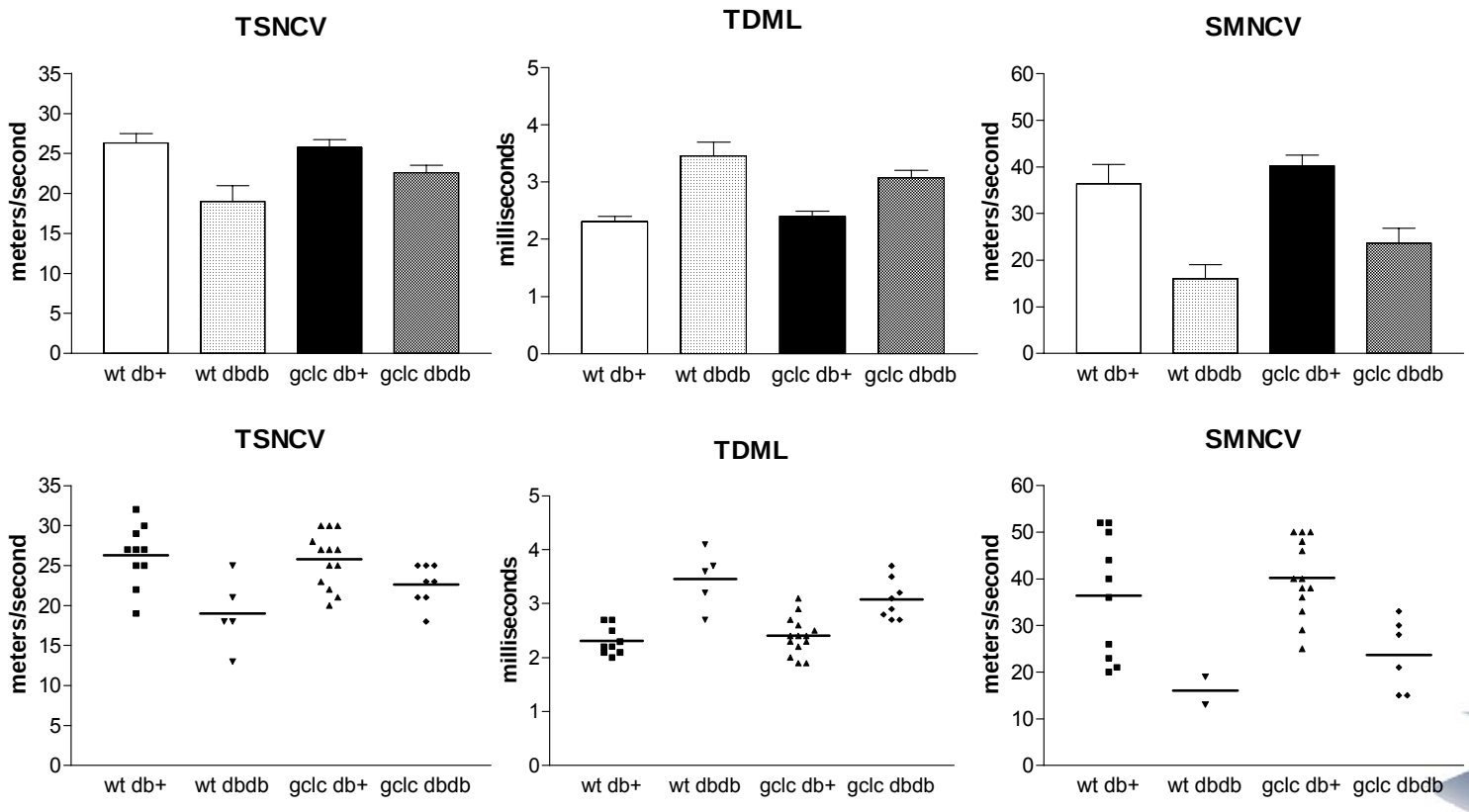
Nerve Conduction Velocity
GCLC +/- db/db High Fat Mice



No Significant Differences

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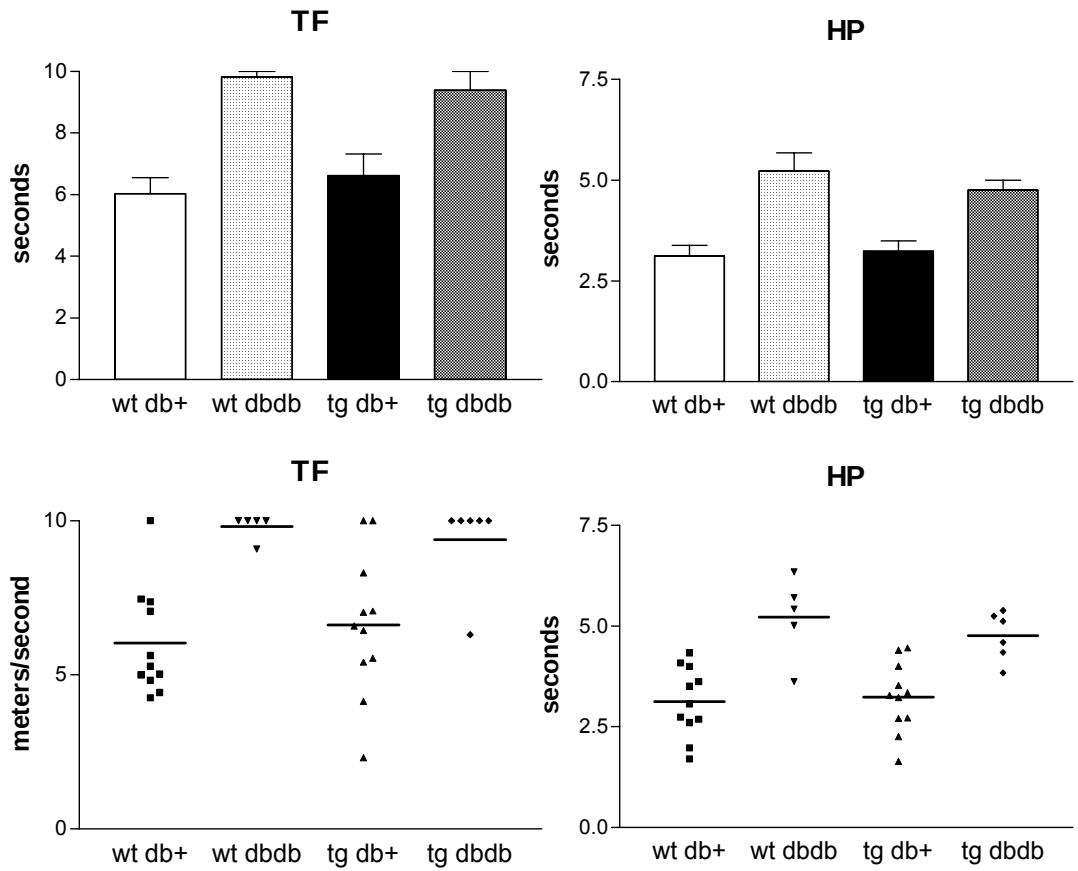
Sensory Tests
GLUT1 tg db/db High Fat Mice



No Significant Differences

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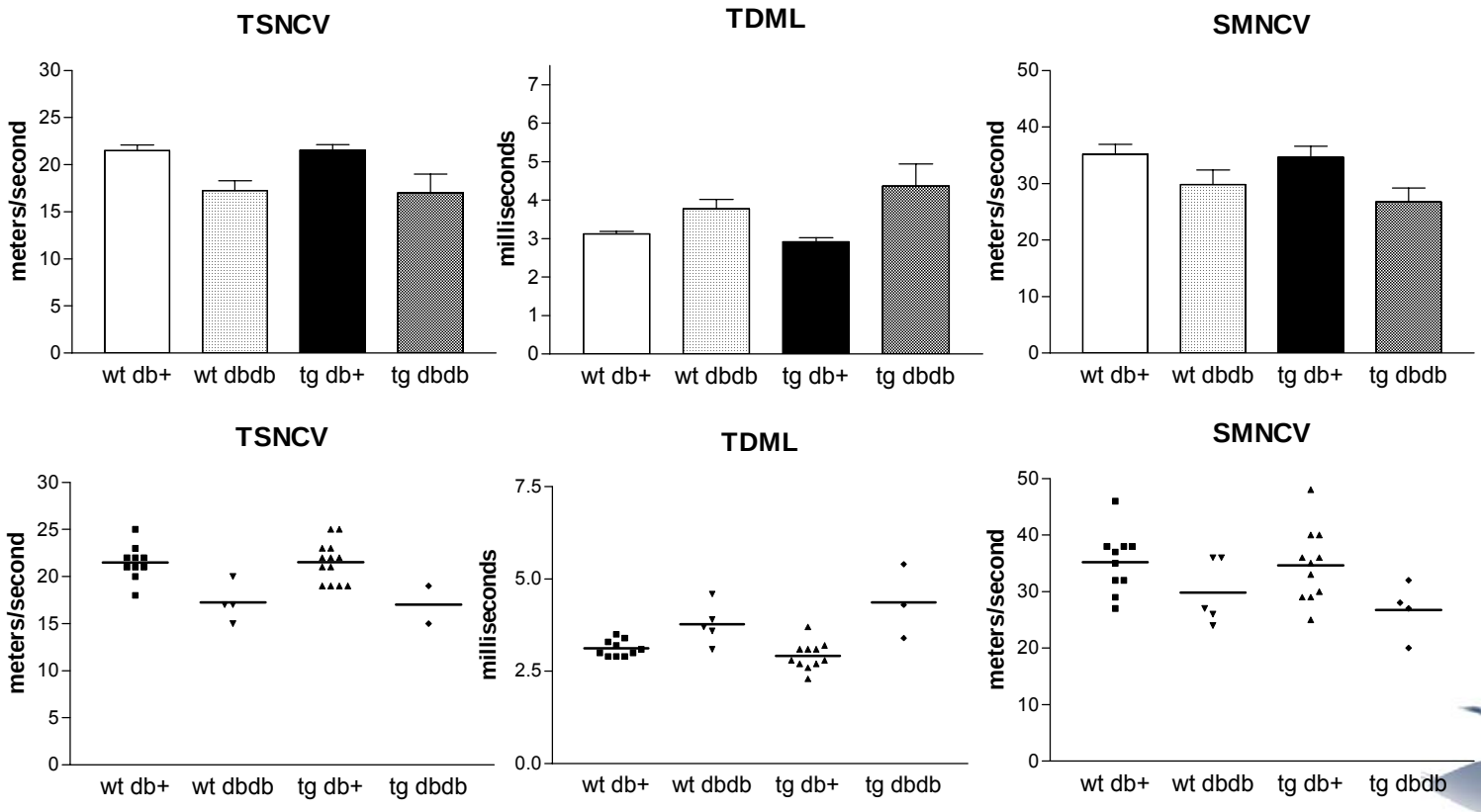
Nerve Conduction Velocity
GLUT1 tg db/db High Fat Mice



No Significant Differences

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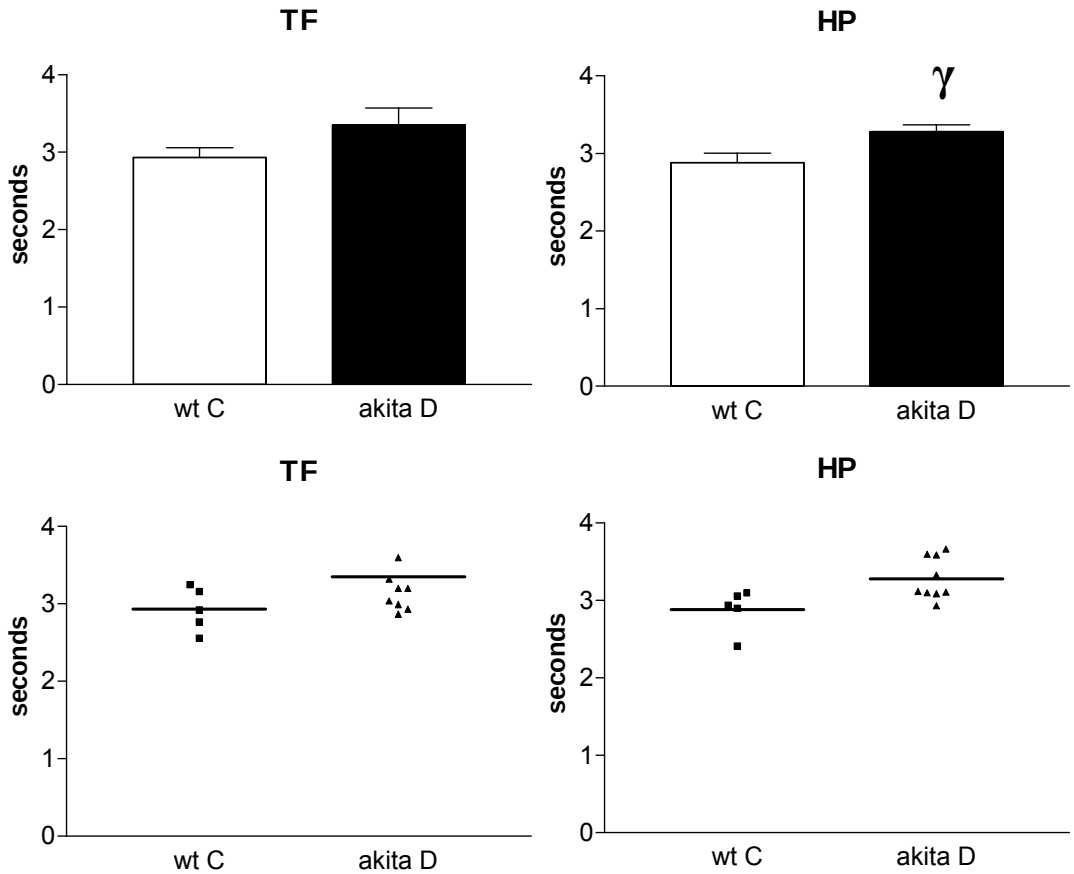
Sensory Tests
Akita Mice



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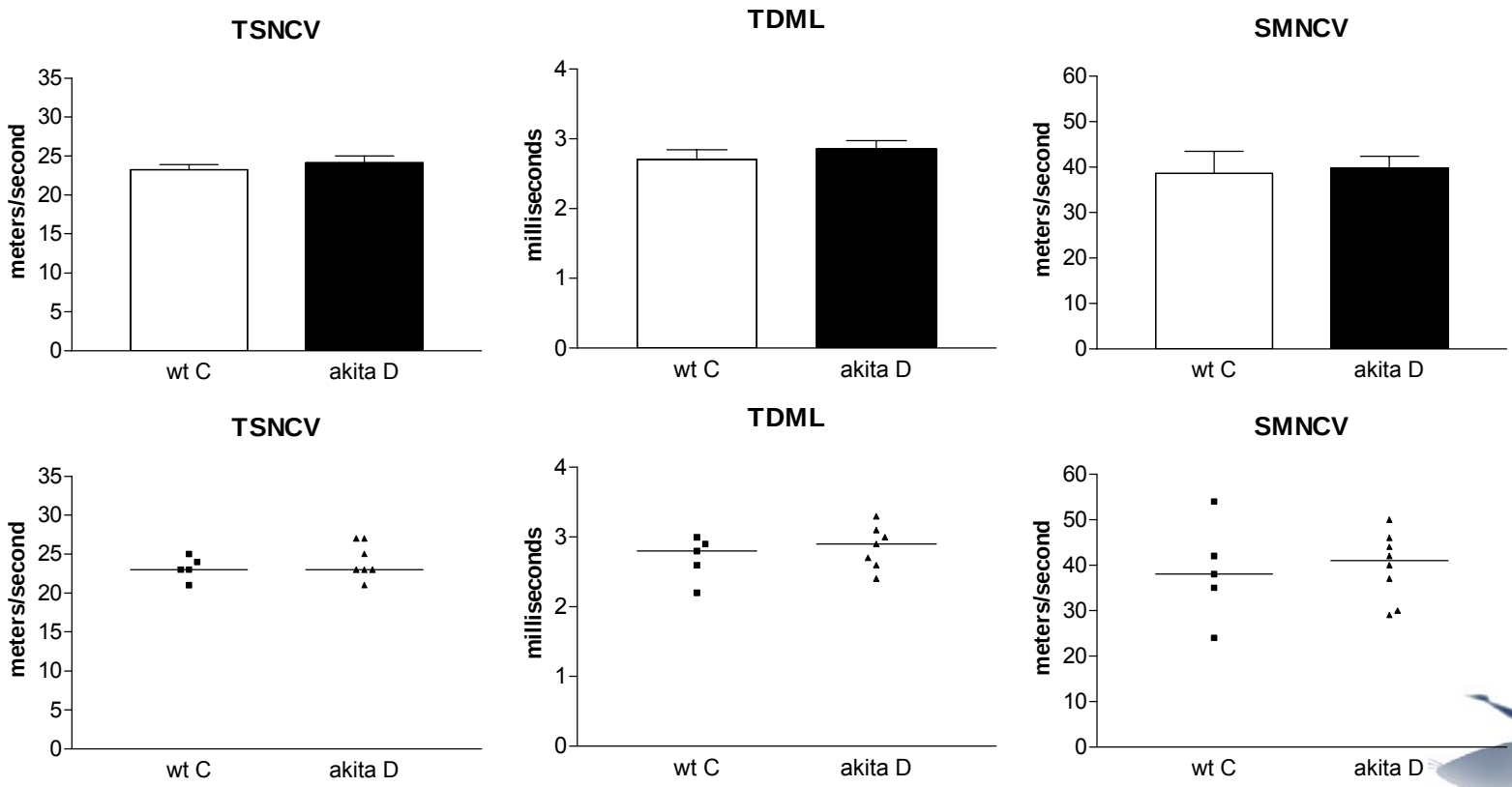
Nerve Conduction Velocity
Akita Mice



No Significant Differences

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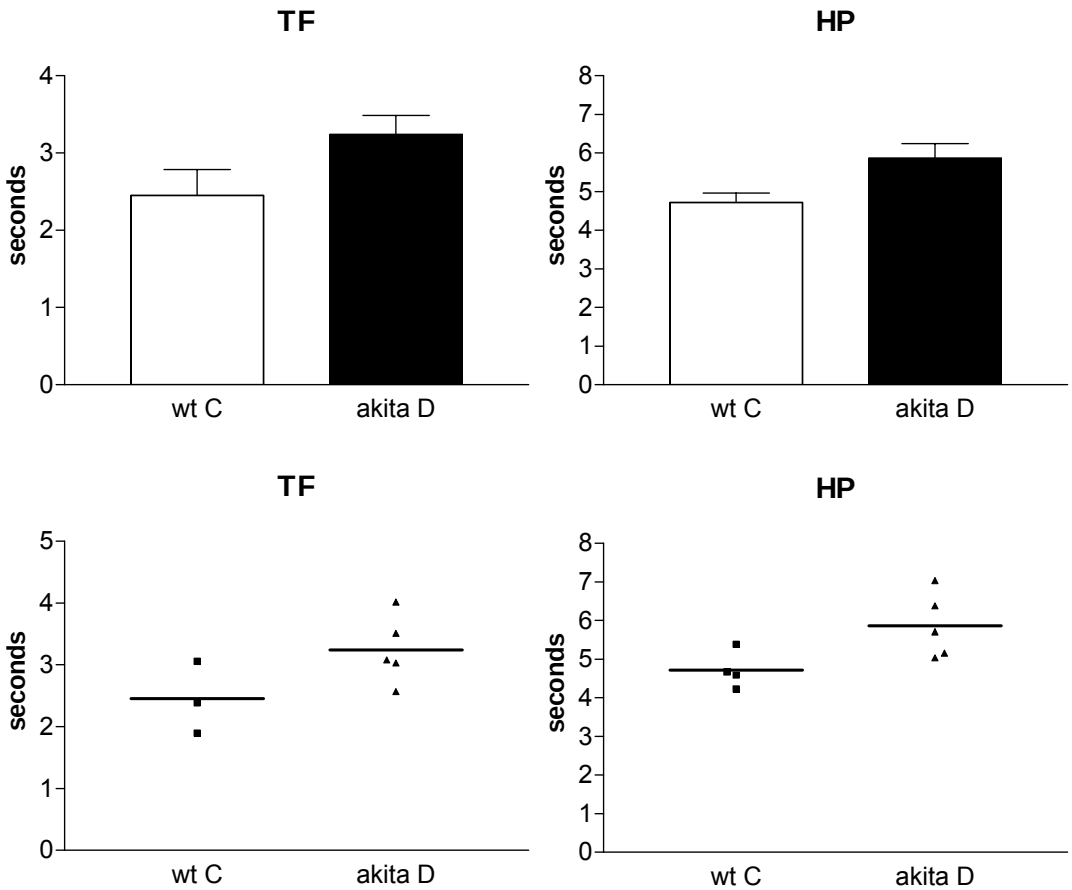
Sensory Tests
Akita Mice ± rosiglitazone



No Significant Differences

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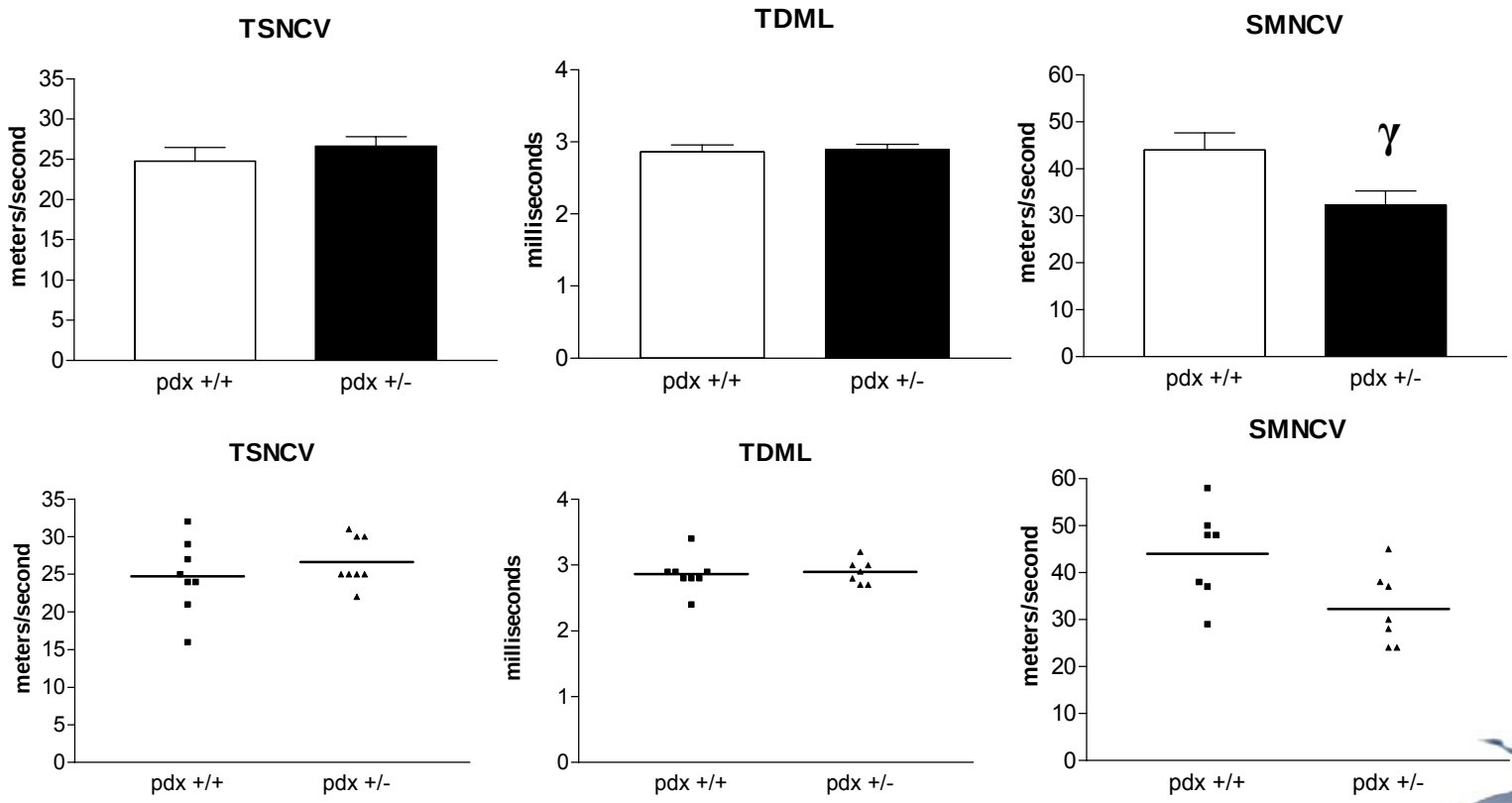
Nerve Conduction Velocity
Pdx Mice



γ P < .05

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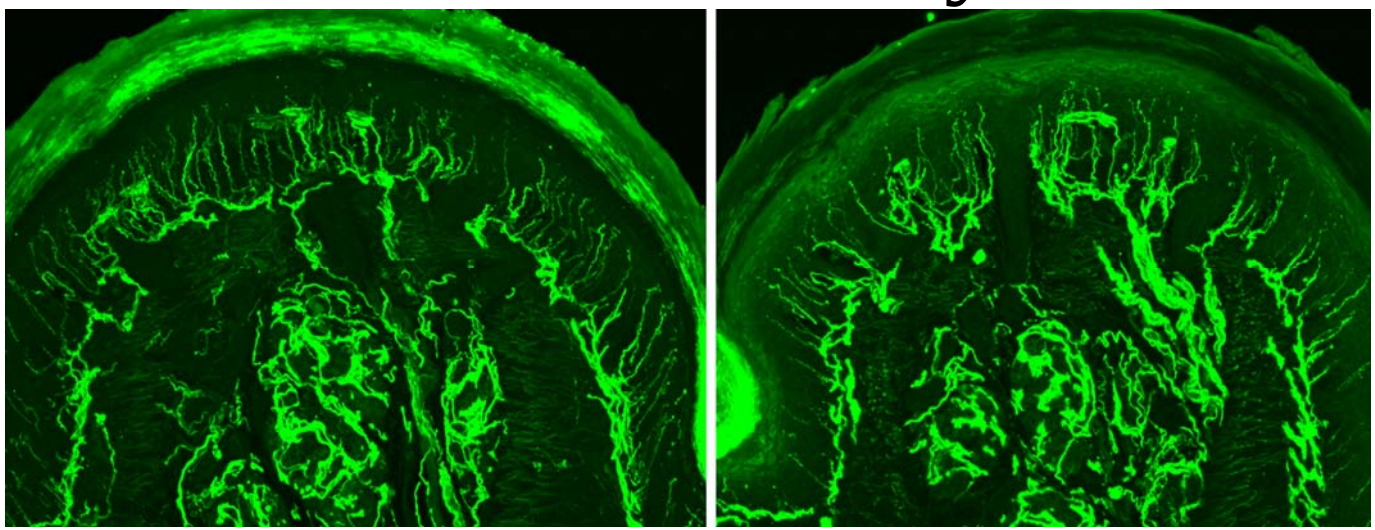
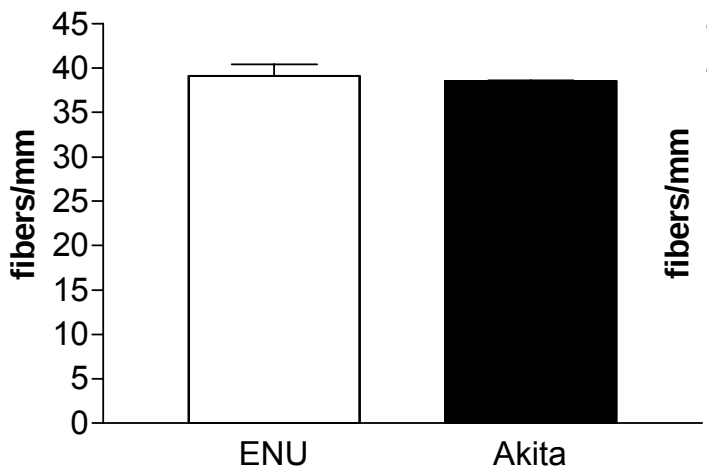
Vanderbilt ENU/Akita Mice
IENF Density



IENF



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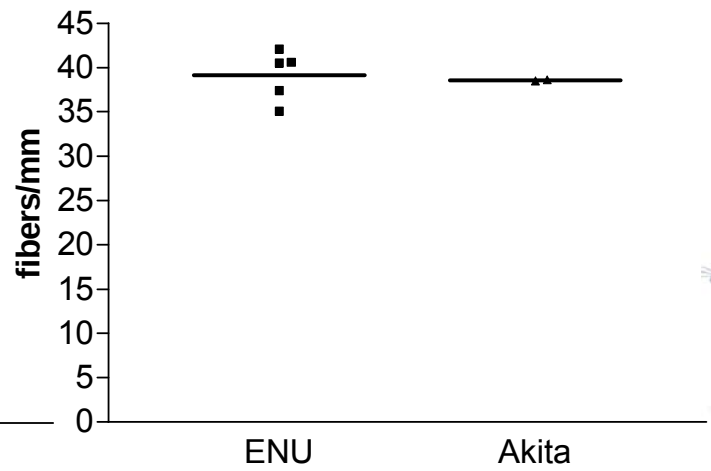

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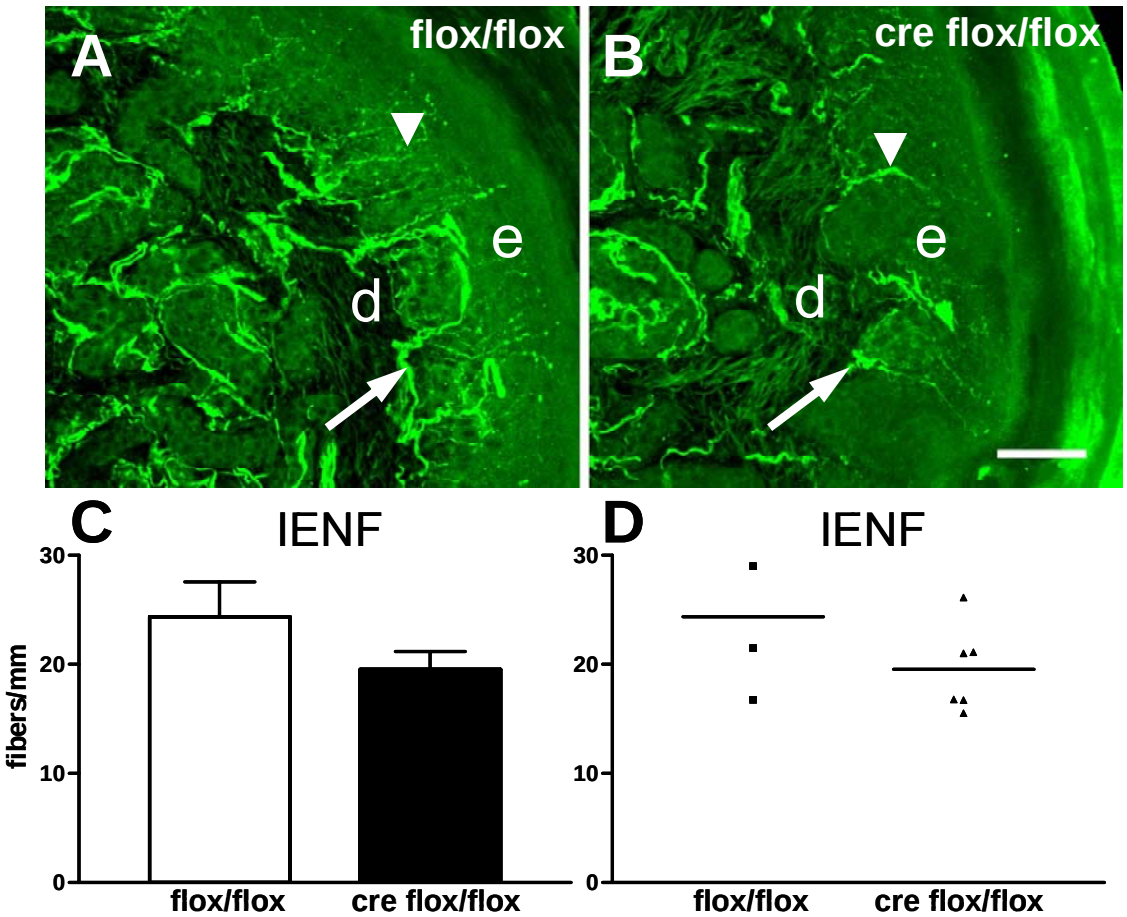
Nestin Cre// SOD2 loxP/loxP
IENF Density



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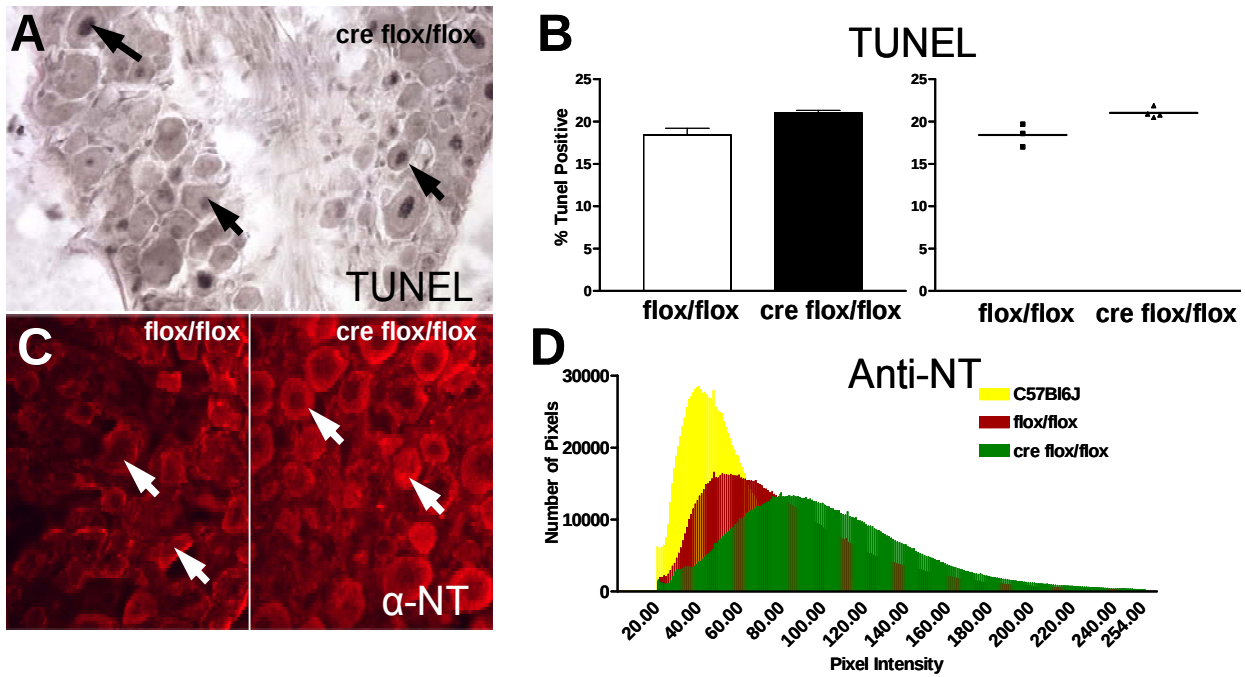
Nestin Cre// SOD2 loxP/loxP TUNEL and Nitrotyrosine IHC



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efeldman@umich.edu
Eva L. Feldman, M.D., Ph.D
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Thanks to NIH/JDRF, EAC and AMDCC Investigators

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C57BLKS db/db mice ± resveratrol

Strain	Group	Body Weight (g)	Plasma glucose (mg/dl)	Glycated hemoglobin (%)
db/+	Untreated	26.0 ± 0.5	88.8 ± 3.8	5.1 ± 0.2
	10 mg/kg resveratrol	26.4 ± 0.6	81.8 ± 4.6	5.7 ± 0.2
	20 mg/kg resveratrol	27.4 ± 0.4	84.1 ± 3.0	5.9 ± 0.2
db/db	Untreated	45.7 ± 0.9*	325.8 ± 12.8*	10.5 ± 0.5*
	10 mg/kg resveratrol	45.4 ± 1.5*	313.7 ± 14.4*†	10.0 ± 0.4*
	20 mg/kg resveratrol	46.6 ± 1.1*	274.4 ± 19.6*†‡	9.1 ± 0.4*†

Values are ± SEM, *$p < 0.05$ versus untreated db+ mice; †$p < 0.05$ versus untreated db/db mice; ‡$p < 0.05$ versus 10 mg/kg RES treated db/db mice.

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C57BLKS db/db mice ± resveratrol

Strain	Group	Body Weight (g)	Glycated Hb (%)	Triglyceride (mg/dl)	SMNCV (m/sec)	TSNCV (m/sec)
db/+	Untreated	26.0 ± 0.5	5.1 ± 0.2	114.1 ± 10.3	23.4 ± 1.2	38.0 ± 1.1
	20 mg/kg res	27.4 ± 0.4	5.9 ± 0.2	122.6 ± 9.4	27.4 ± 0.4	37.4 ± 3.4
db/db	Untreated	45.7 ± 0.9*	10.5 ± 0.5*	169.9 ± 15.1*	16.9 ± 0.9*	26.0 ± 2.7*
	20 mg/kg res	46.6 ± 1.1*	9.1 ± 0.8*	161.9 ± 18.1*	15.1 ± 0.5*	22.8 ± 2.2*

Evaluation of peripheral nerve function in db/+ and db/db mice treated with/without RES Values are ± SEM,

*$p < 0.05$ versus untreated db+ mice.

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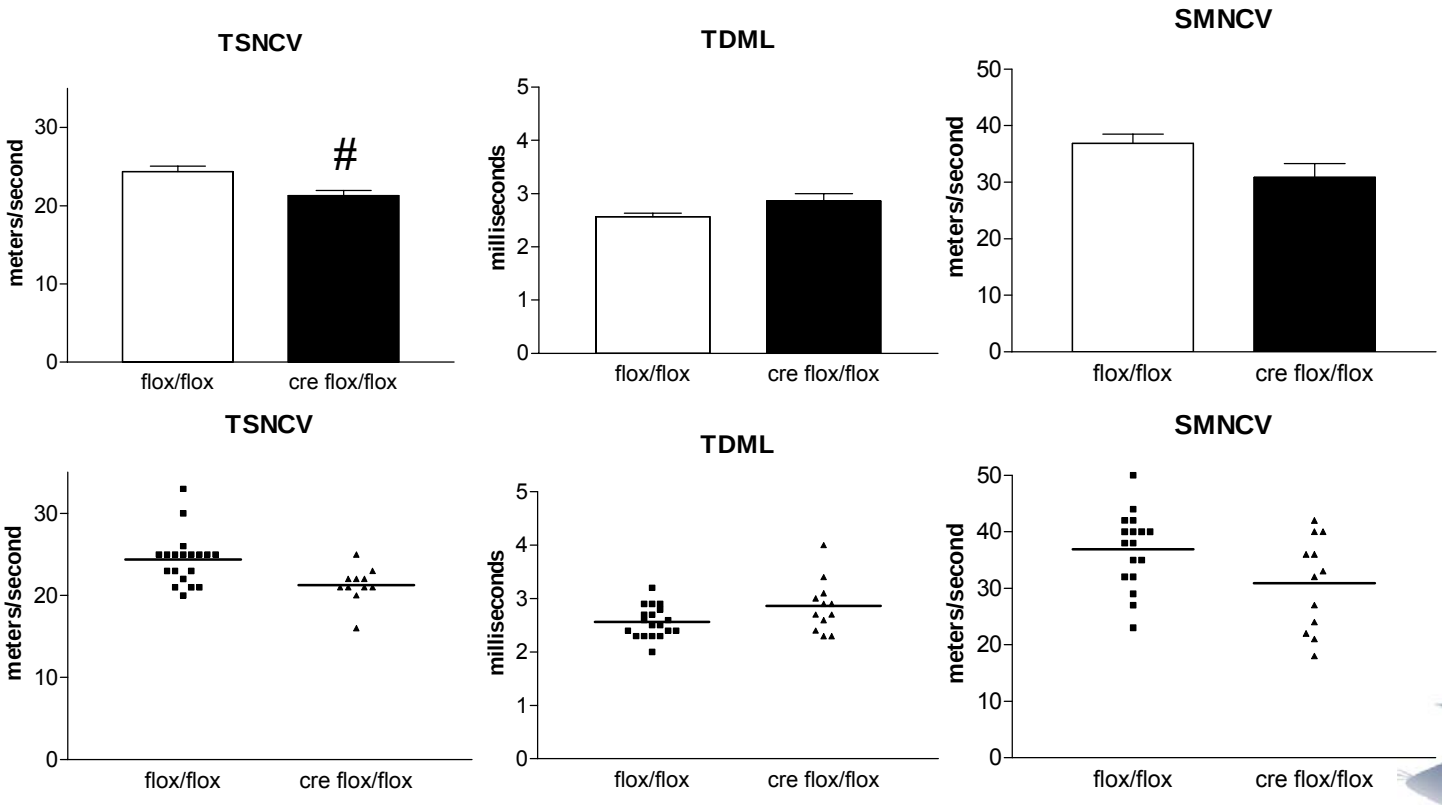
Nerve Conduction Velocity
Nestin Cre// SOD2 loxP/loxP Mice



 # P < .01

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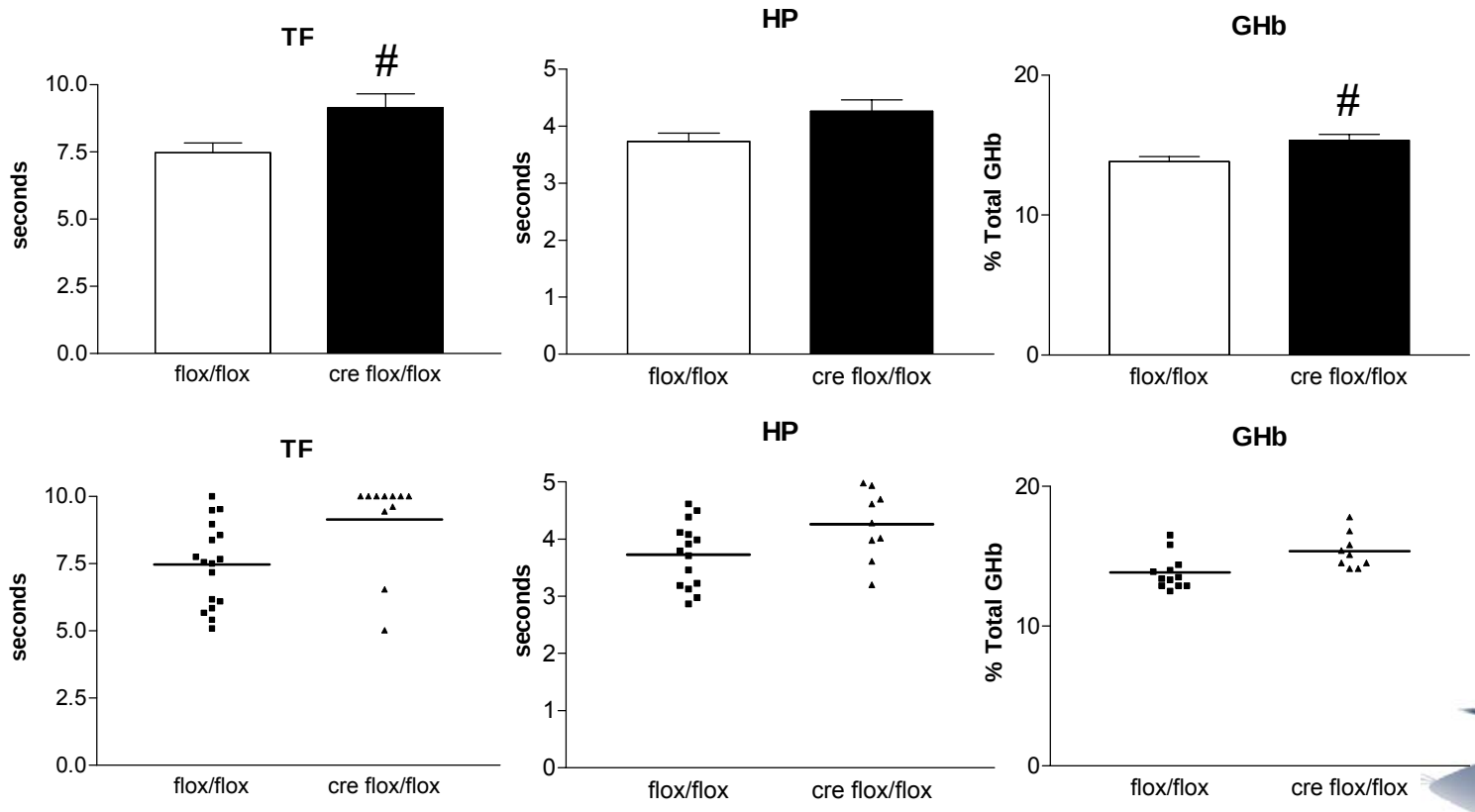
Sensory Tests
Nestin Cre// SOD2 loxP/loxP Mice



 # P < .01

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