

Table S1

	Non-Diabetic (Mean±SEM, N=15-18)		Diabetic (Mean±SEM, N=15-17)	
	Weight (Kg)	Blood Glucose (mg/dL)	Weight (Kg)	Blood Glucose (mg/dL)
Days	Comparisons made between non-diabetic and diabetic (**P<0.001)			
Day 0	3.115 ± 0.057	176.595 ± 11.625	3.253 ± 0.068	176.595 ± 11.625
Day 10	3.3 ± 0.048	175.800 ± 7.900	3.082 ± 0.079	394.000 ± 18.794 ***
Day 20	3.24 ± 0.054	162.684 ± 5.728	3.118 ± 0.074	383.412 ± 19.491 ***

Table S2

Days	Sham		Ischemic		Neuroischemic	
	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic
	% of original wound size (Mean±SEM, N=15-18)		% of original wound size (Mean±SEM, N=5-6)			
	Comparisons made between non-diabetic and diabetic (**P<0.001, *P<0.05)					
Day 12	100±0.0	100±0.0	100±0.0	100±0.0	100±0.0	100±0.0
Day 15	86.67±2.04	104.67±3.04 ***	84.91±1.6	94.29±2.57 *	90.54±2.14	94.8±3.2
Day 20	53±3.23	78.801±4 ***	76.5±3.4	89.00±4.45 *	81.92±2.28	86±3.9

Table S3

	Baseline		Sham		Ischemic		Neuroischemic	
	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic
	(Mean±SEM, N=15-18)	Fold Change Over Non-Diabetic Baseline (Mean±SEM, N=15-17)	Fold Change Over Non-Diabetic/Diabetic Baseline (Mean±SEM, N=5-6)					
	Comparisons made between non-diabetic and diabetic (***P<0.001, **P<0.01, *P<0.05)							
Infiltration								
Extent	1.0±0.028	1.325±0.067 *	2.92±0.20	1.8±0.15 ***	2.7±0.106	1.546±0.22 ***	4.06±0.21	2.26±0.32 **

Table S4

M1/M2 Ratio	Baseline		Sham		Ischemic		Neuroischemic	
	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic
	(Mean±SEM, N=7)	Fold Change Over Non-Diabetic Baseline (Mean±SEM, N=6)	Fold Change Over Non-Diabetic/Diabetic Baseline (Mean±SEM, N=3-6)					
	Comparisons made between non-diabetic and diabetic (***P<0.001, **P<0.01, *P<0.05)							
	0.338±0.021	1.142±0.084 ***	0.653±0.054	1.405±0.048 ***	0.597±0.062	1.414±0.099 ***	0.637±0.091	1.611±0.196 **

Table S5

Genes	Baseline		Sham		Ischemic		Neuroischemic	
	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic
	(Mean±SEM, N=15-18)	Fold Change Over Non-Diabetic Baseline (Mean±SEM, N=15-17)	Fold Change Over Non-Diabetic/Diabetic Baseline (Mean±SEM, N=5-6)					
	Comparisons made between non-diabetic and diabetic (***P<0.001, *P<0.05)							
IL-8	2.78±0.91	12.27±2.74 **	3.36±1.49	0.78±0.38	6.33±2.7	0.996±0.25 *	1.9±0.49	0.35±0.15 *
CXCR1	4.46±1.65	54.45±9.85 ***	6.85±2.74	0.53±0.13 *	18.24±5.3	1.03±0.18 **	7.6±3.2	0.39±0.20 *
IL-6	2.6±0.75	7.12±1.09 *	1.044±0.248	0.269±0.08 **	5.25±2.3	1.41±0.28 **	2.76±1.1	0.16±0.02 *
SP	2.88±1.06	2.78±1.39	0.38±0.054	0.23±0.11	0.42±0.09	0.26±0.03	0.63±0.18	0.24±0.09 *
NK1R	0.75±0.158	0.39±0.06 *	1.6±0.63	3.57±1.722	7.17±5.0	8.2±4.73	0.1±0.04	0.047±0.014
NEP	1.98±0.44	2.89±1.13	4.38±1.2	2.99±0.96	2.5±1.09	1.36±0.356	7.99±4.5	0.96±0.25 *
NPY	2.22±0.82	3.13±0.97	1.425±0.66	0.47±0.152	0.64±0.25	0.12±0.026 *	0.67±0.22	0.13±0.04 *
NPY2R	4.49±1.83	13.104±4.23	2±0.83	0.36±0.28	4.037±2.79	0.46±0.078	2.26±2.05	0.11±0.03
NPY5R	5.25±2.1	14.85±4	0.66±0.22	0.17±0.006	1.13±0.363	0.3±0.067	1.77±1.56	0.11±0.04
DPPIV	2.3±0.96	6.14±1.5 *	1.04±0.17	0.51±0.085 *	1.51±0.198	0.97±0.17 *	0.58±0.07	0.6±0.073

Table S6

Proteins	Baseline		Sham		Ischemic		Neuroischemic	
	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic	Non-Diabetic	Diabetic
	(Mean±SEM, N=15-18)	Fold Change Over Non-Diabetic Baseline (Mean±SEM, N=15-17)	Fold Change Over Non-Diabetic/Diabetic Baseline (Mean±SEM, N=5-6)					
	Comparisons made between non-diabetic and diabetic (**P<0.001, *P<0.05)							
IL-8	1.0±0	1.103±0.04	1.39±0.12	1.27±0.07	1.49±0.15	1.081±0.13 *	1.037±0.28	0.9±0.04
CXCR1	1.0±0	0.99±0.08	1.19±0.15	1±0.07	1.6±0.21	1.215±0.15	1.74±0.10	1.45±0.19
IL-6	1±0.084	1.13±0.07	1.53±0.11	1.036±0.07 *	1.24±0.12	0.825±0.05 *	1.96±0.16	1.21±0.11 *
SP	1±0.034	0.609±0.04 ***	0.94±0.05	1.22±0.09	0.84±0.13	1.26±0.10	1.36±0.17	0.92±0.08 *
NK1R	1.0±0	1.05±0.04	0.96±0.14	1.082±0.11	1.2±0.07	1.73±0.12 *	1.15±0.122	0.88±0.08
NEP	1.0±0	1.16±0.23	1.146±0.13	1.22±0.13	2.21±0.74	1.55±0.27	1.6±0.18	1.58±0.13
NPY	1±0.104	0.6±0.06 ***	1.231±0.11	1.42±0.09	0.86±0.14	1.35±0.17	1±0.5	1.55±0.22
NPY2R	1.0±0	1.01±0.16	1.097±0.25	1.25±0.17	1.84±0.54	1.406±0.18	1.04±0.12	1.63±0.06 *
NPY5R	1.0±0	0.98±0.12	0.99±0.15	1.18±0.18	1.23±0.23	1.56±0.04	1.33±0.16	1.58±0.12
DPPIV	1.0±0	1.68±0.34 *	0.9±0.09	0.855±0.69	1.076±0.21	0.71±0.15	0.91±0.15	0.76±0.02

Table S7

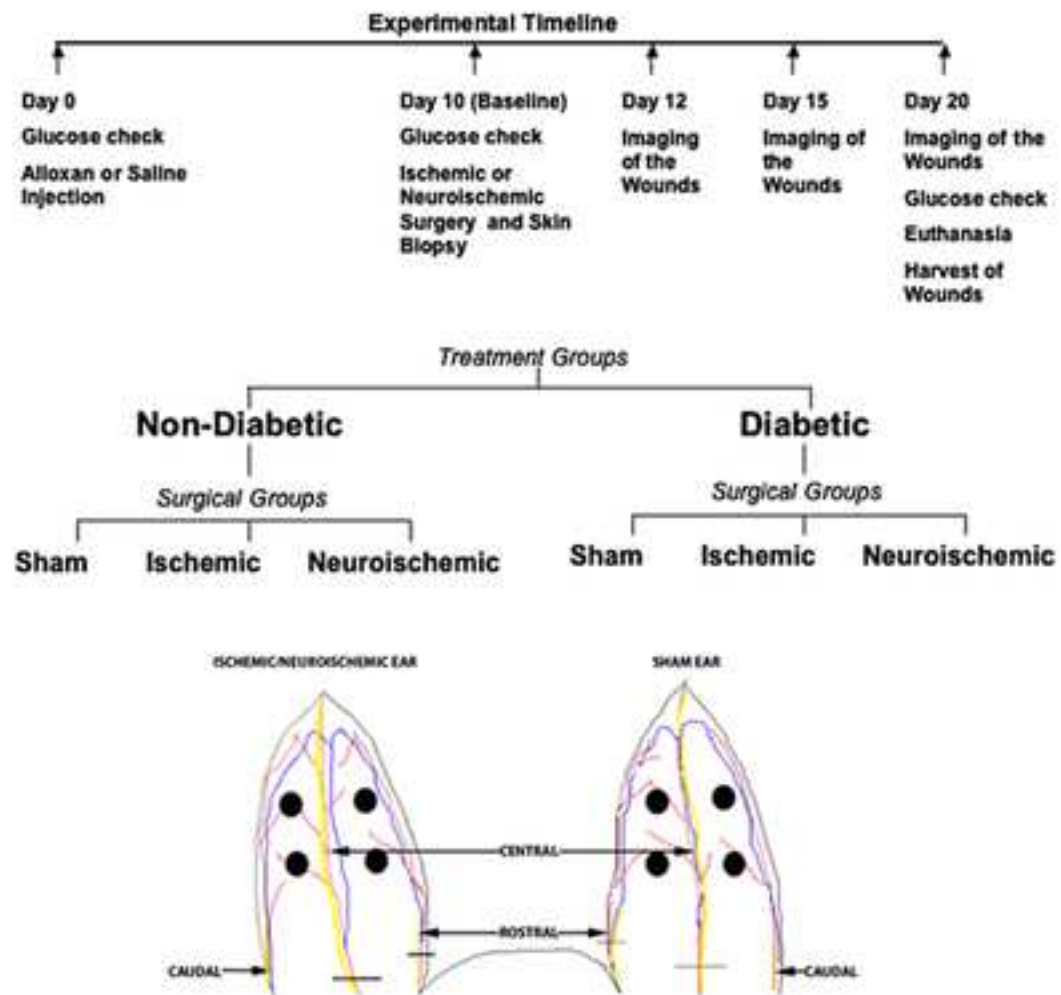
Gene	Q-RT-PCR Primer Sequences
IL-8	F: CTC TGC TGG CTG CCC TAC R: CTG ACA CGT CTC CTG GAT CA
CXCR1	F: GGC GCT GTC TCT GAT TTT GT R: GGC TGG AAT TGT TTG GAG AA
IL-6	F: GTC AGC CTG ATG GAG AAC CT R: GGA TGA AGT GGA TCG TGG TC
Substance P (Pre-pro-Tachykinin A)	F: TGT GTC TCA GGG CTG AAA TG R: TAT GGA ACC ACA AAC CGT GA
NK1R	F: TTG GCC CAC AAG AGA ATG AGG ACA R: AGT ACC ACT CGT TGT GGA CAG CAT
NEP	F: TGT GCA CAG TCC AGG CAA TTT CAG R: TTC TGT AGA TCA CAA AAC CCG GCA
NPY (Pre-pro-NPY)	F: CCA GCC CAG AGA CAC TGA TT R: ACA TTG CAG GGT CTT CAA GC
NPY2R	F: AAA TGA TGG TGT GTG TGG TGG TGG R: AGT TGC TGT TCA TCC AGC CGT AGA
NPY5R	F: TAA CAG CCA ACC ACG GCT ACT TCT R: TCC TGC AGT TCC ACA AGA CTG TGA
DPPIV	(SABiosciences Qiagen, Valencia, CA Cat # PPH00035A)
Beta-actin	F: TGT ATG AAG GCT TTT GCT CTC C R: CTG GTC TCA AGT CAG TGT ACA GGT

Table S8

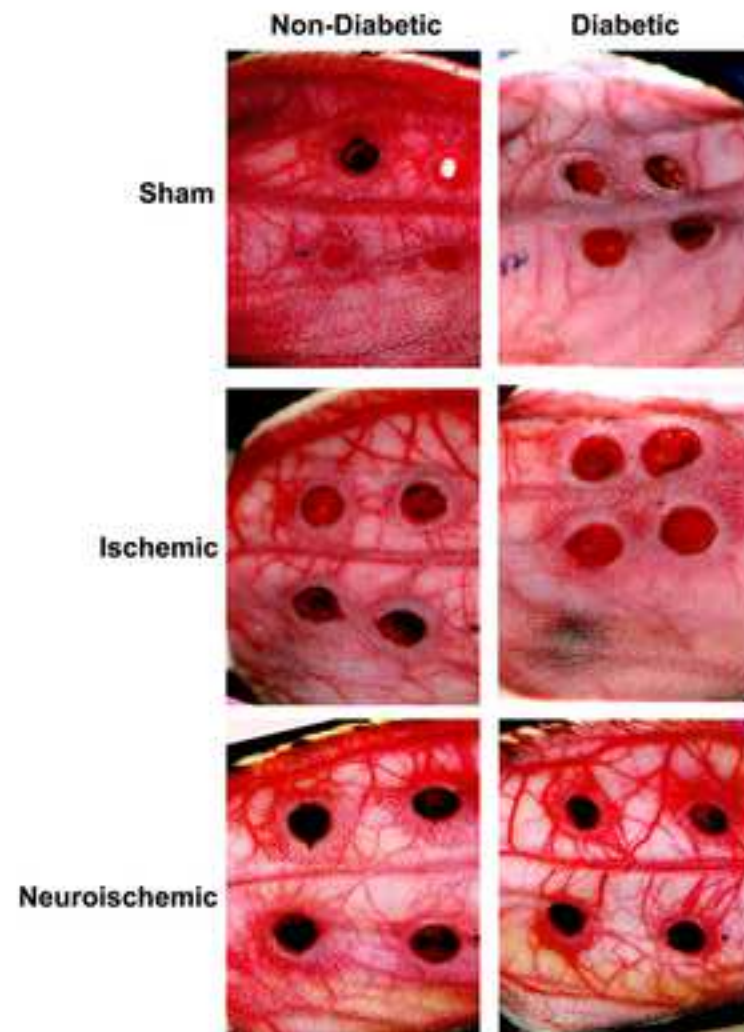
Western Blot Reagents							
Antibody	Company	Catalog number	Dilution	Secondary Antibody	Company	Catalog number	Dilution
CXCR1	R&D Systems, MN	MAB 330	1:100	Goat-Anti Mouse	R&D Systems, MN	HAF007	1:500
NK1R	SCBT, CA	SC 14115	1:100	Donkey-Anti Goat	SCBT, CA	SC2020	1:500
NEP	R&D Systems, MN	MAB 1182	1:100	Rabbit-Anti Mouse	Sigma Aldrich, MO	A9044	1:500
NPY2R	SCBT, CA	SC 14736	1:100	Donkey-Anti Goat	SCBT, CA	SC2020	1:500
NPY5R	SCBT, CA	SC 23843	1:100	Donkey-Anti Goat	SCBT, CA	SC2020	1:500
DPPIV	R&D Systems, MN	AF 1180	1:250	Donkey-Anti Goat	SCBT, CA	SC2020	1:500
Immunohistochemistry Reagents							
Antibody	Section Type	Company	Catalog number	Dil	Secondary Antibody	Company	Catalog number
IL8	OCT-Fr	Abcam, MA	AB 10769	1:10	Anti-goat	R&D Systems, MN	CTS008
IL6	FFPE	R&D Systems, MN	MAB 2061	1:50	Anti-mouse	Vector Labs, CA	PK6102
Sub P	FFPE	SCBT, CA	SC 21715	1:25	Anti-rat	SCBT, CA	SC 2019
NPY	FFPE	Abcam, MA	AB 1583	1:1000	Anti-sheep (1:100)	Millipore, MA	AP 184B
CD177	FFPE	Lifespan Biosciences	LS-B1953	1:15	Anti-mouse	Vector Labs, CA	PK6102
CD3	FFPE	BD Biosciences	550367	1:15	Anti-mouse	Vector Labs, CA	PK6102
CD18	OCT-Fr	AbD Serotec, NC	MCA1780	1:15	Goat Anti-mouse (1:400)	AbD Serotec, NC	STAR117D488GA
HLA-DR	OCT-Fr	Abcam, MA	ab49388	1:100	Donkey Anti-mouse (1:400)	Jackson Labs, ME	715-507-003
CD206	OCT-Fr	AbD Serotec, NC	MCA2155	1:100	Donkey Anti-mouse (1:400)	Jackson Labs, ME	715-507-003

FFPE= Formalin Fixed Paraffin Embedded, OCT-Fr= OCT-Frozen, SCBT= Santa Cruz Biotechnology Note: CD18-CD206 and CD18-HLA-DR were co-stained using standardized protocol. DAPI (4',6-diamidino-2-phenylindole, dihydrochloride), LIFE TECHNOLOGIES CORPORATION Cat# D1306 was used (1:1000) for staining nuclei

S1A



S1B

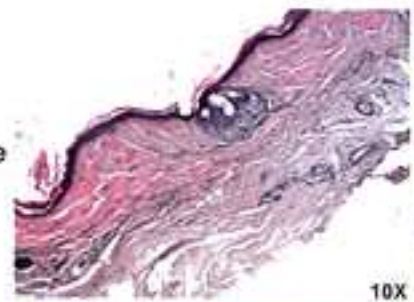


S2

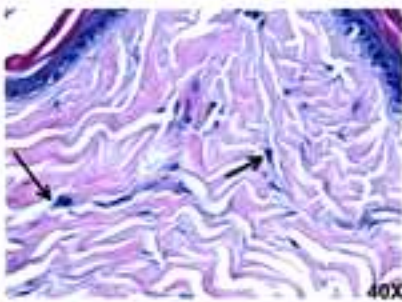
Non-Diabetic

Diabetic

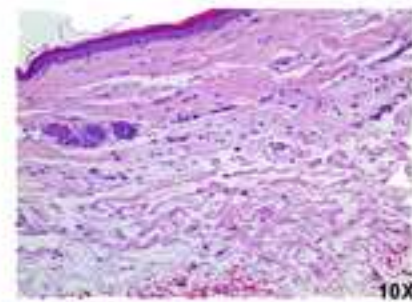
Baseline



10X



40X

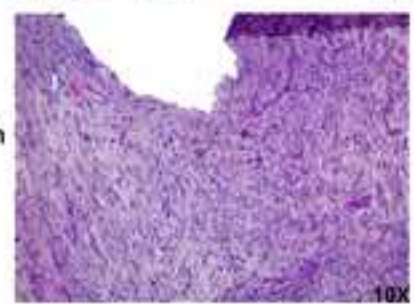


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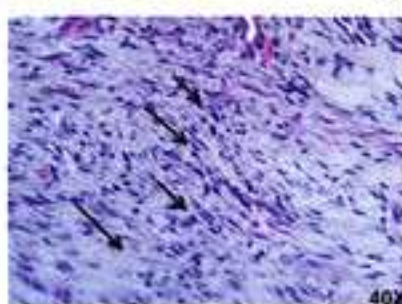


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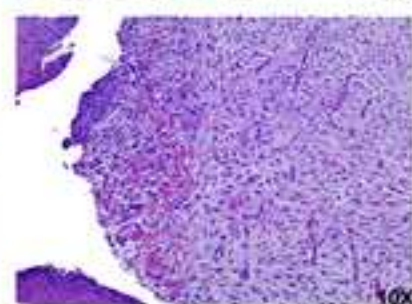
Sham



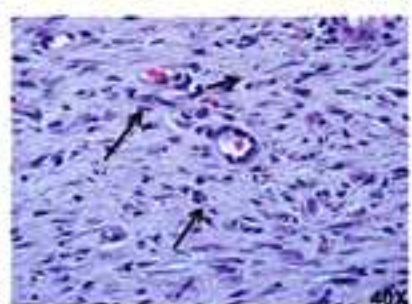
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40X

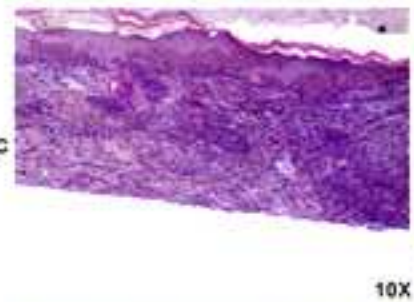


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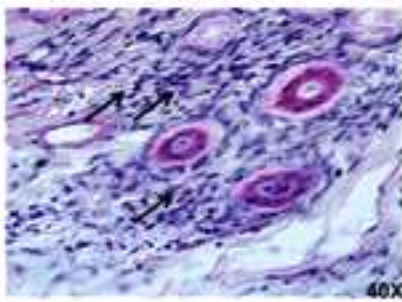


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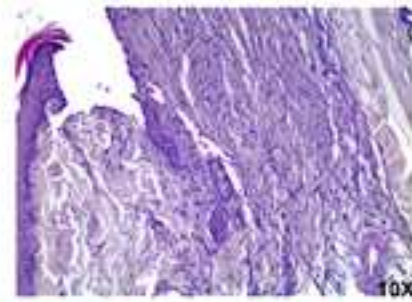
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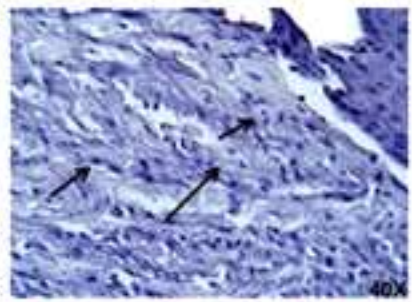
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40X

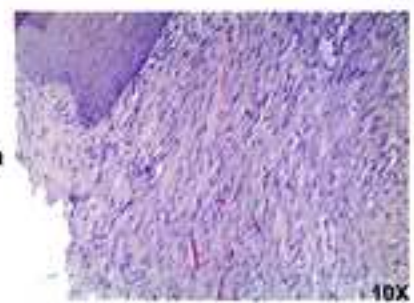


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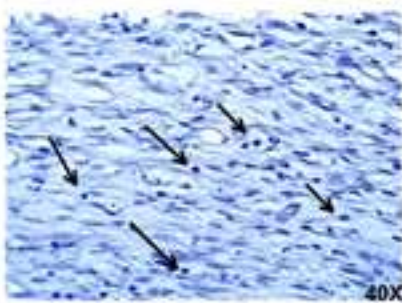


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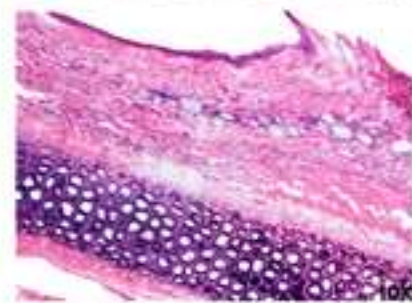
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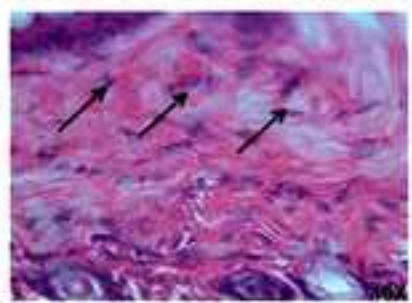
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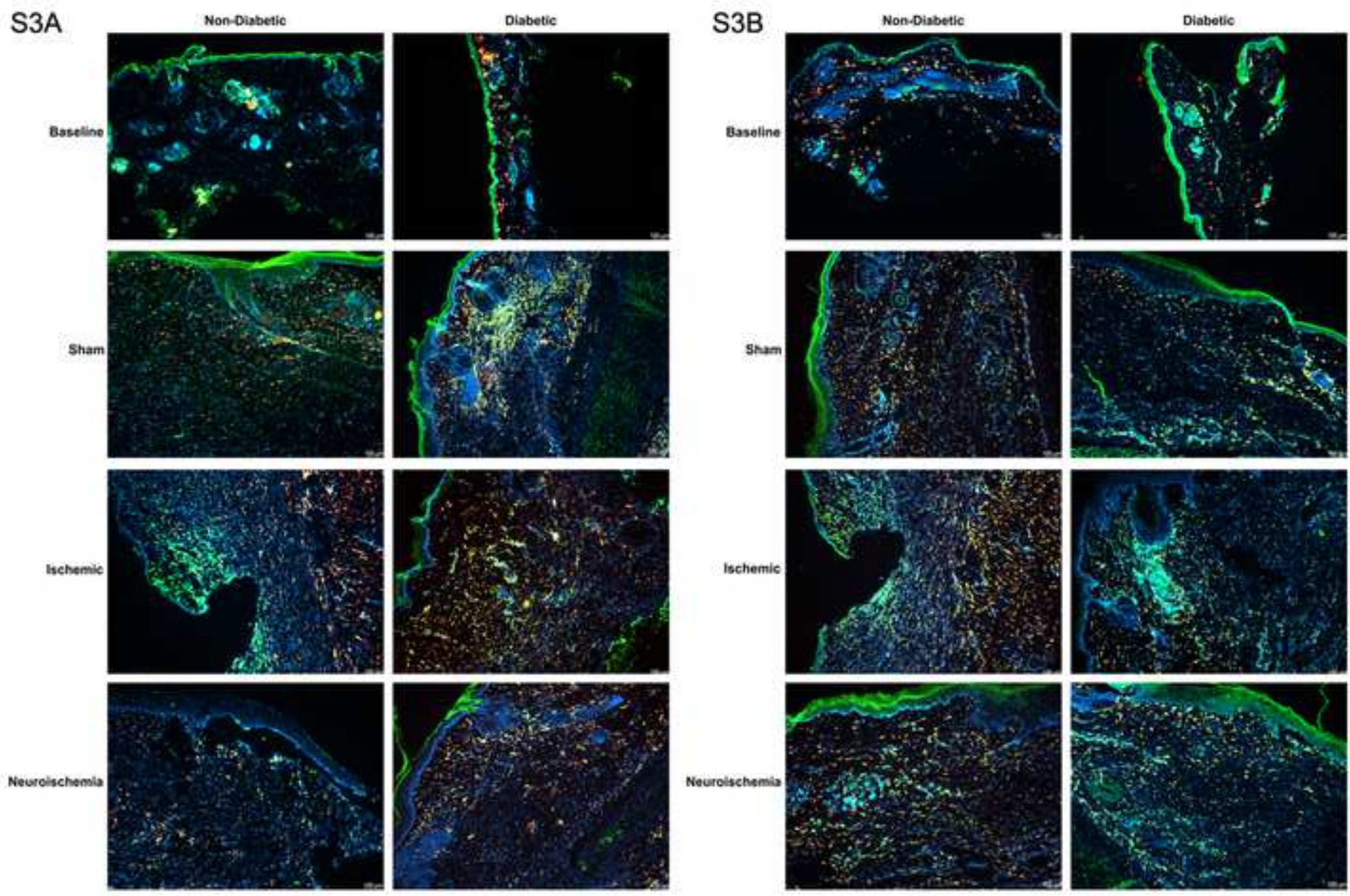
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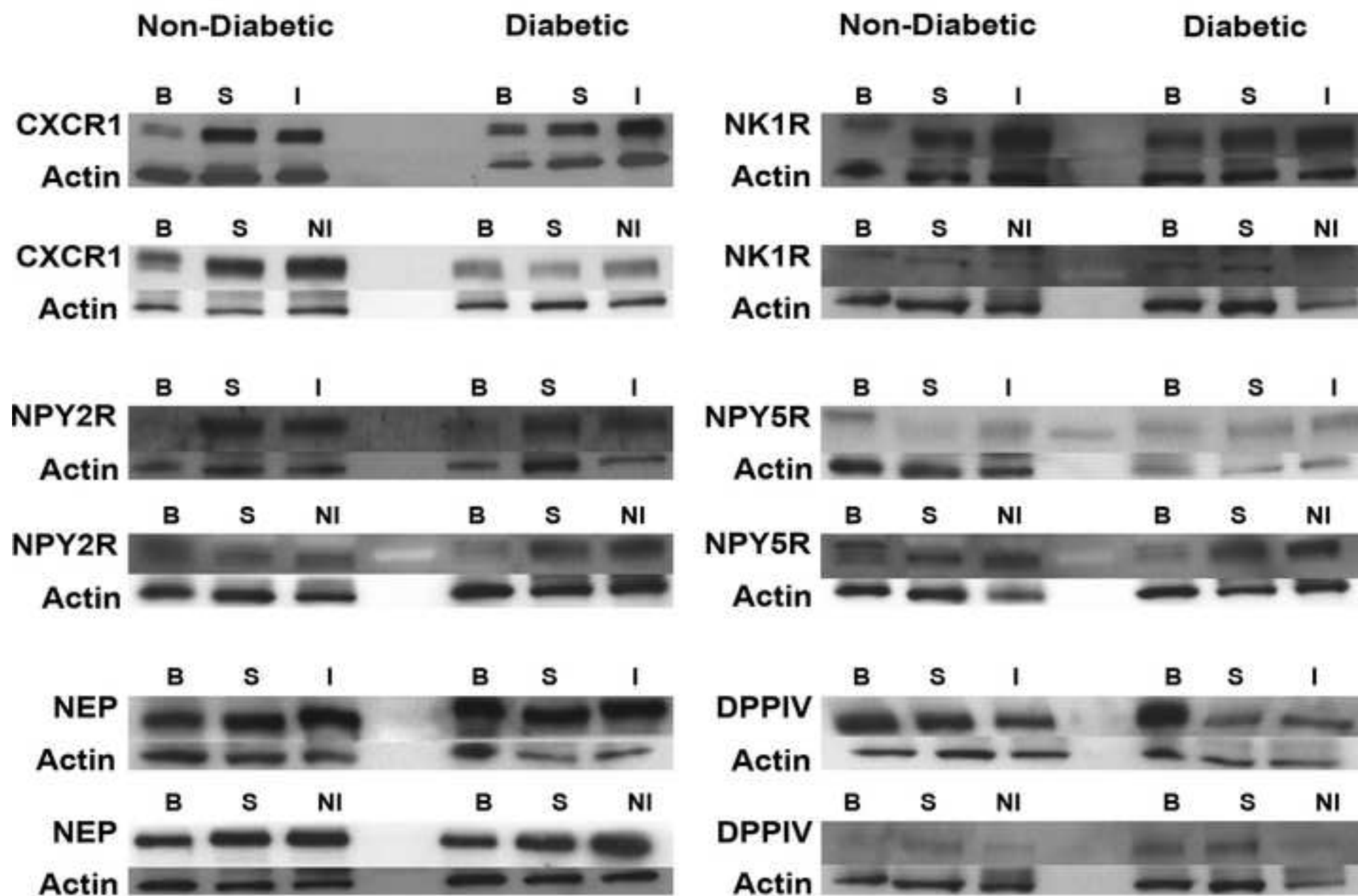


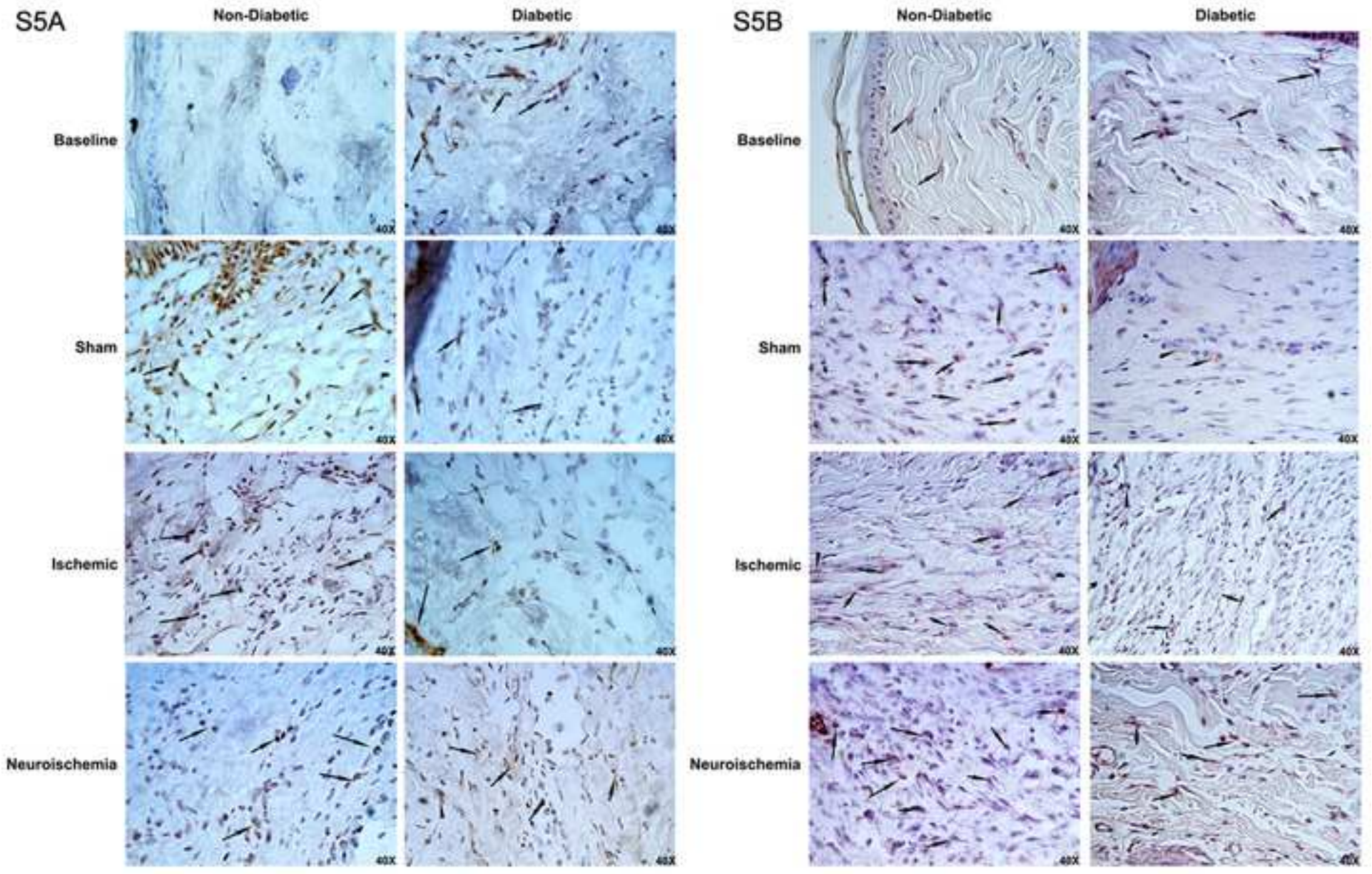
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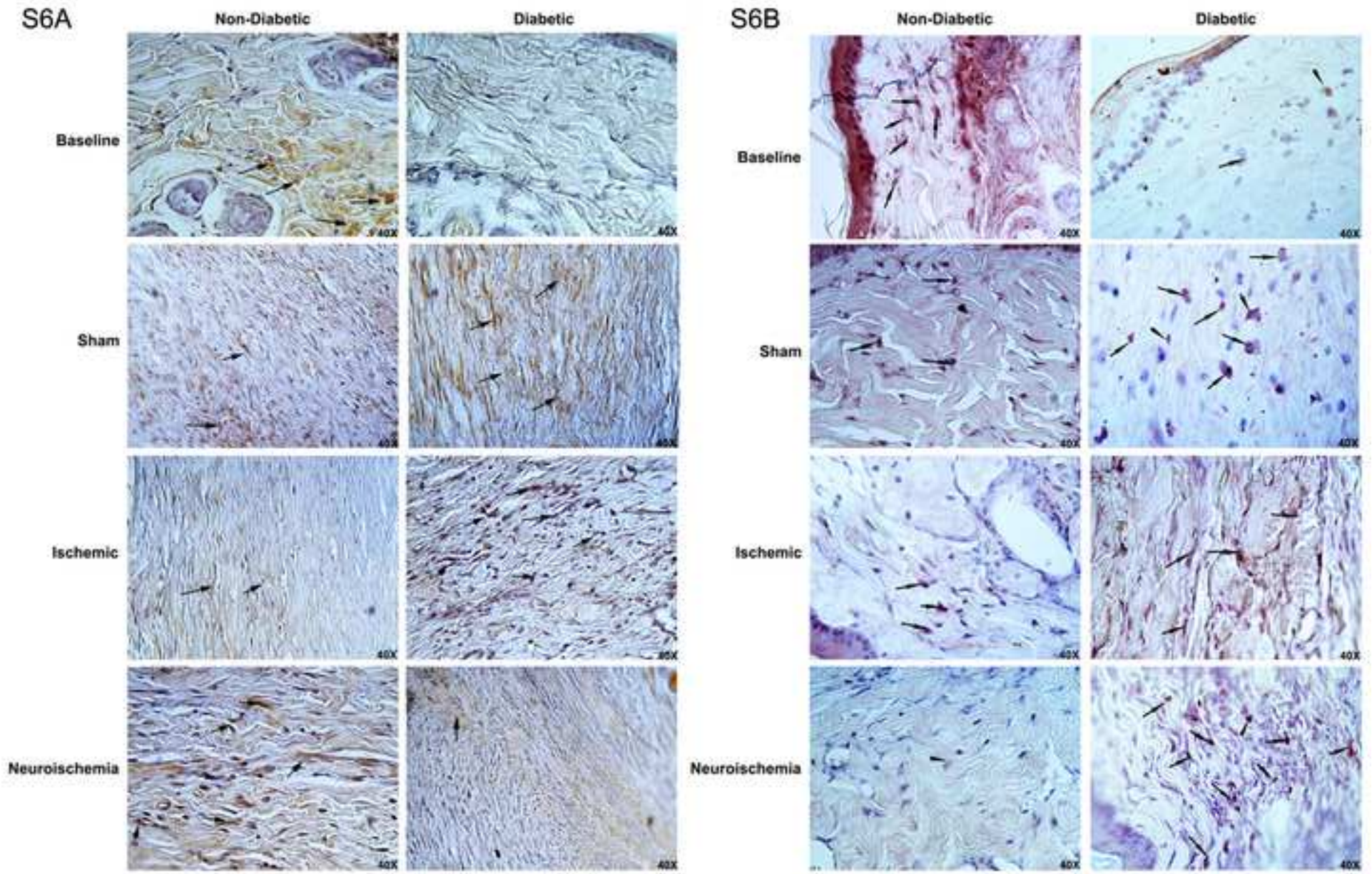


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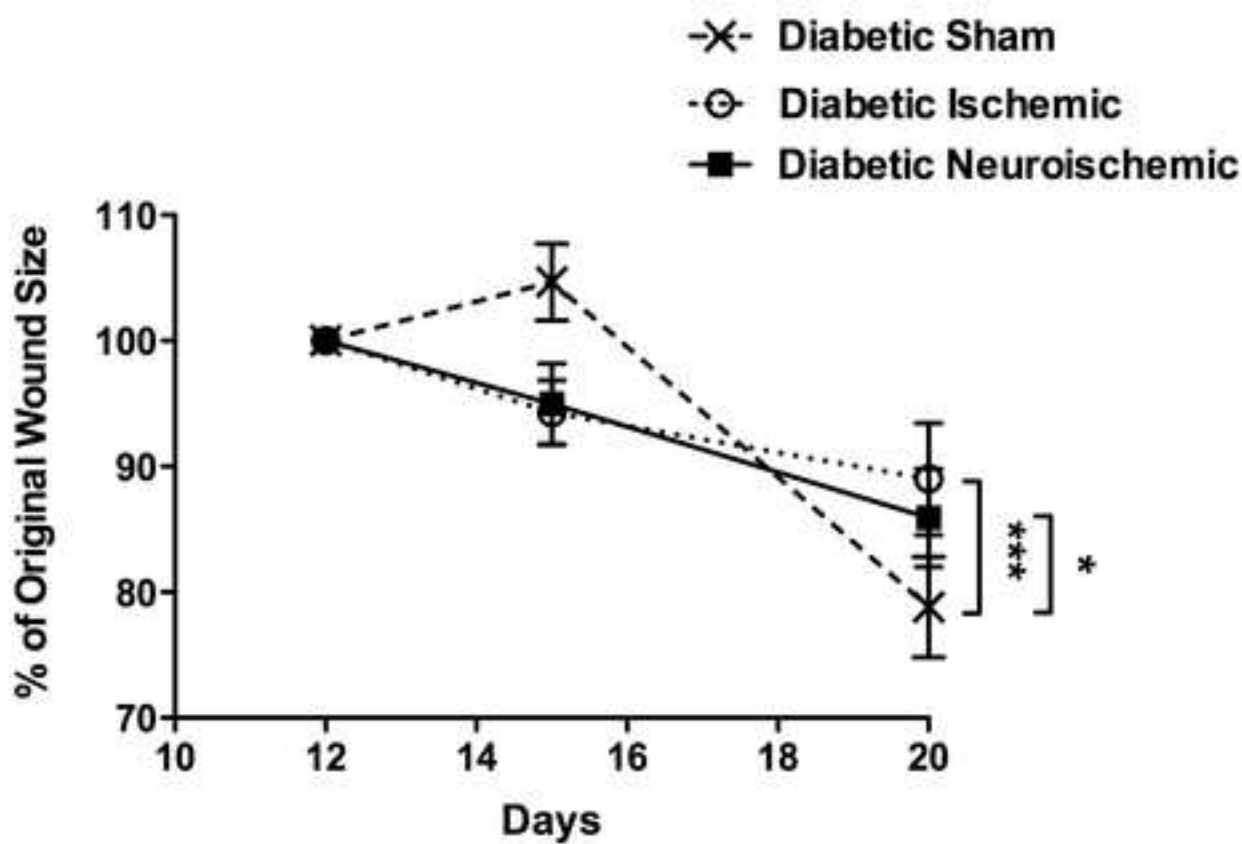
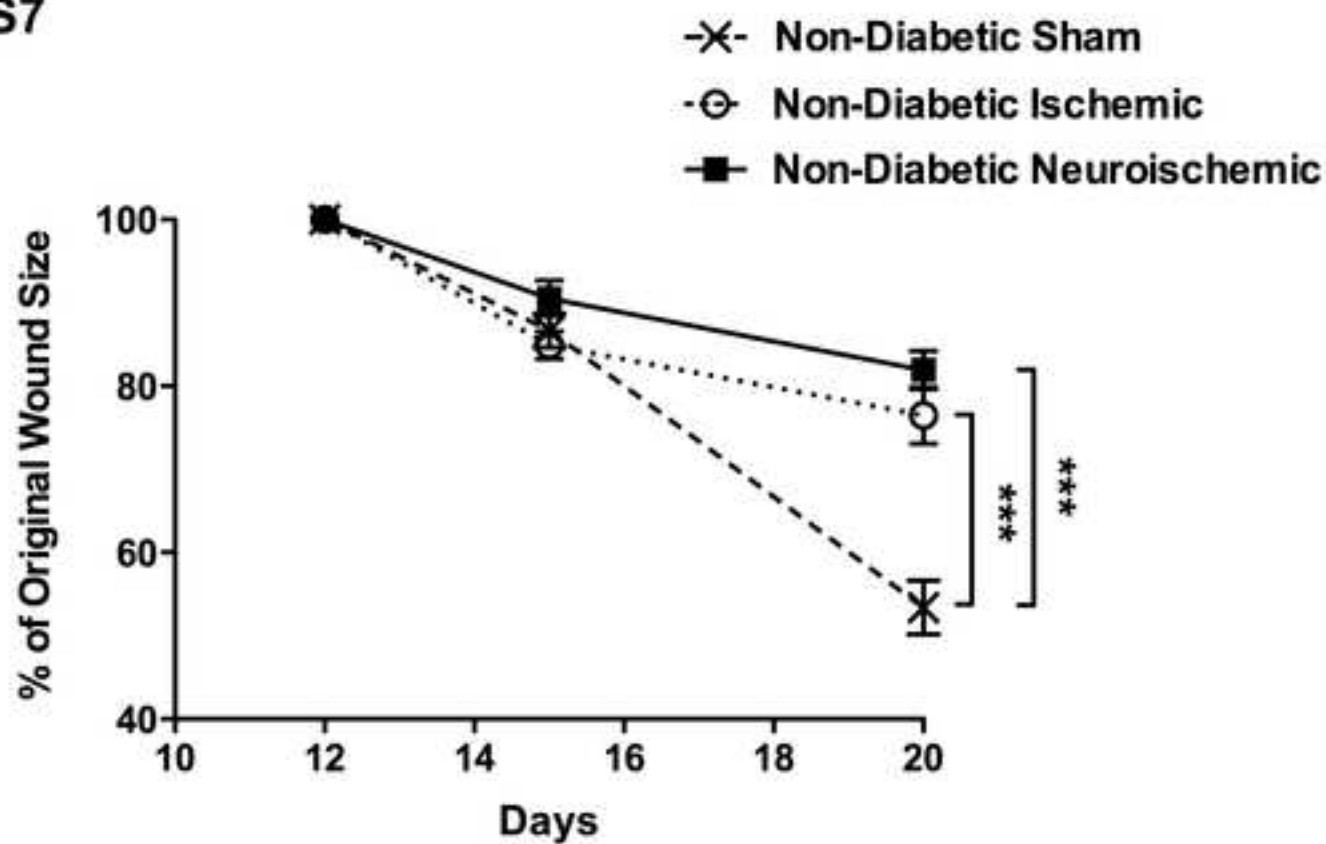


S4

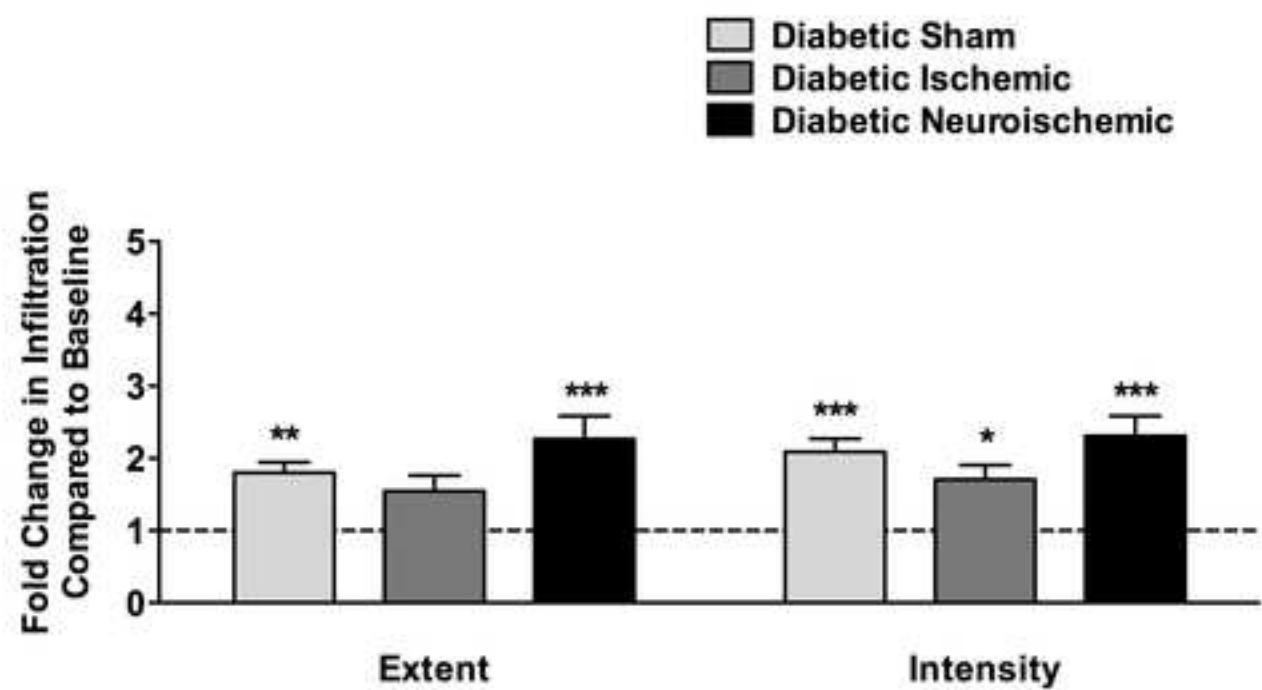
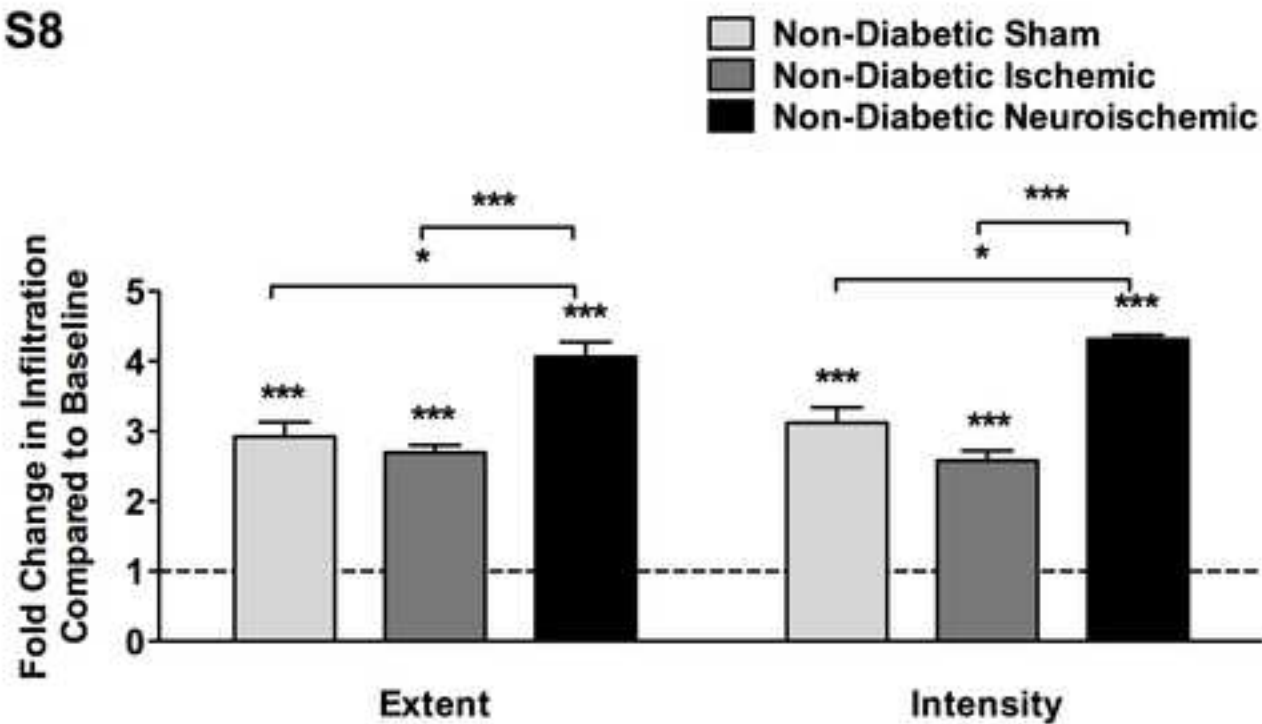




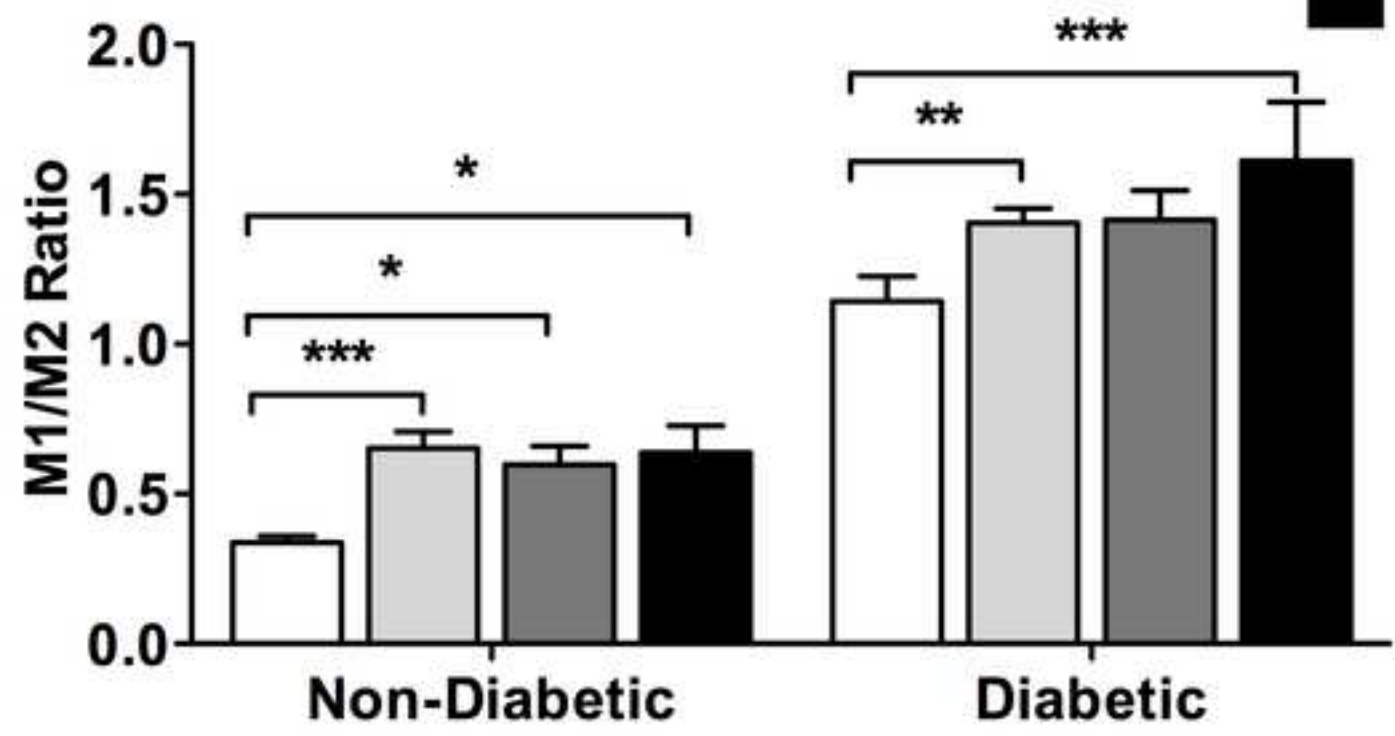
S7



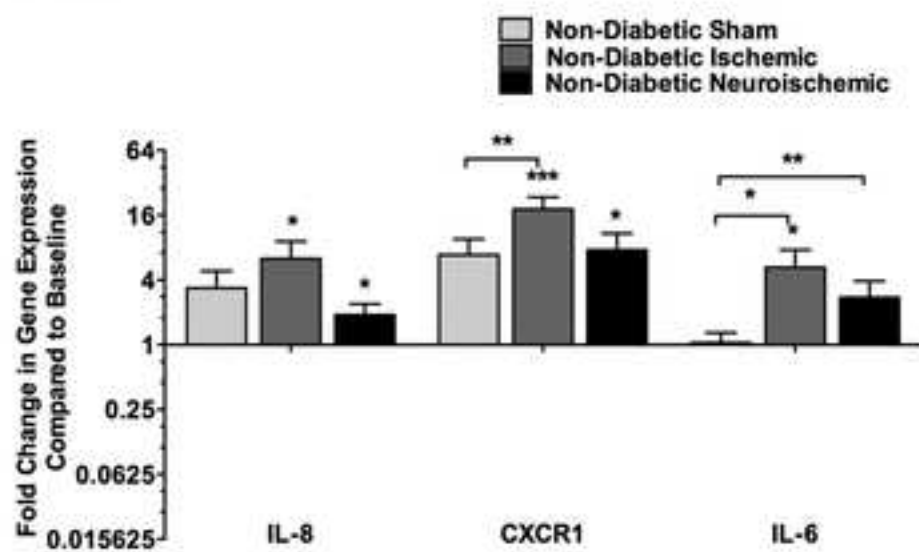
S8



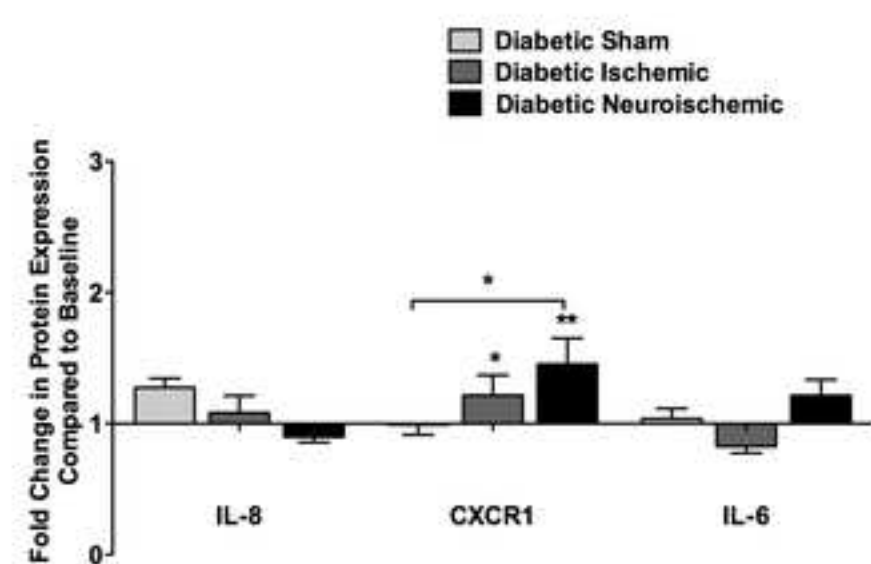
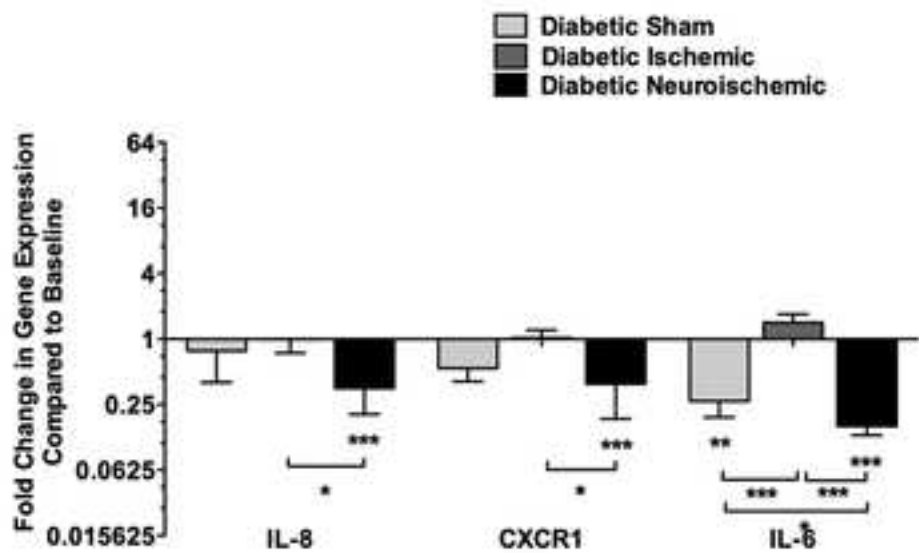
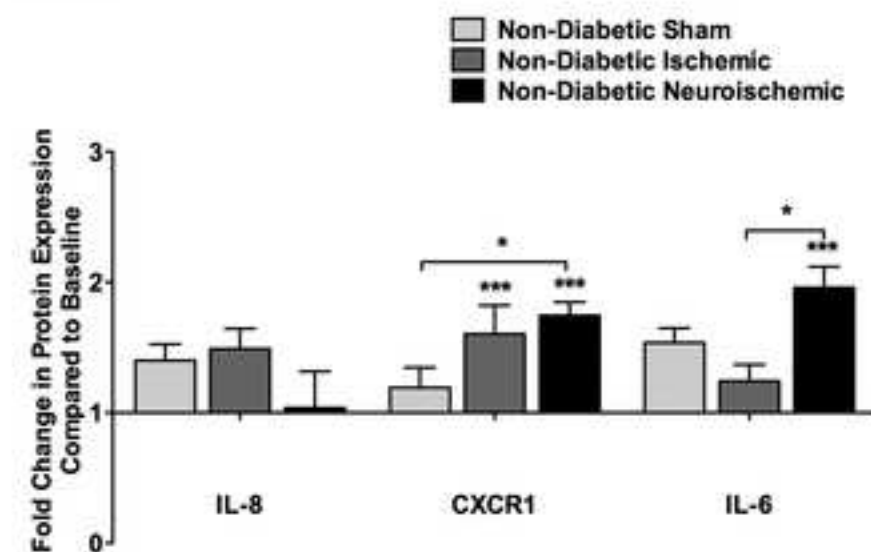
S9



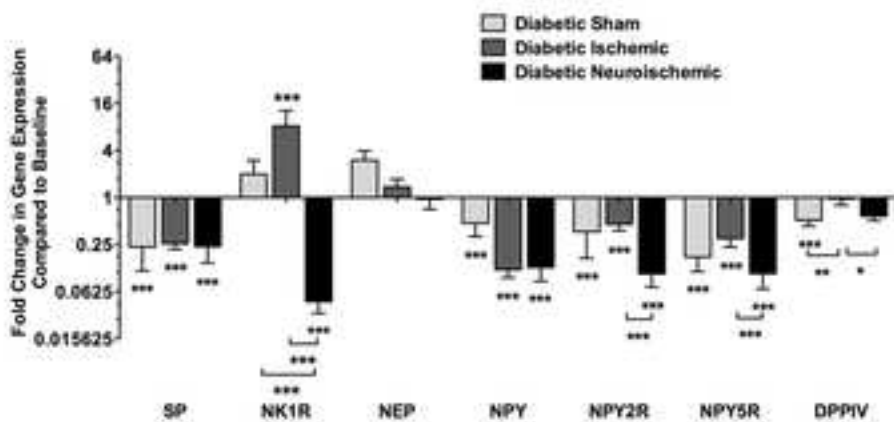
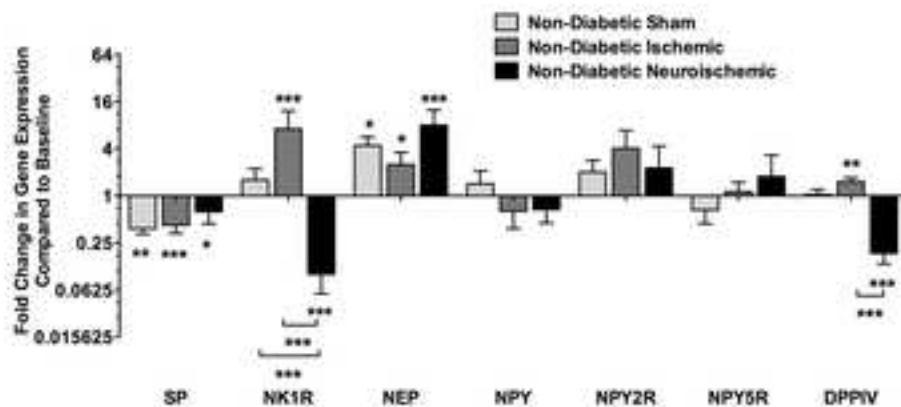
S10A



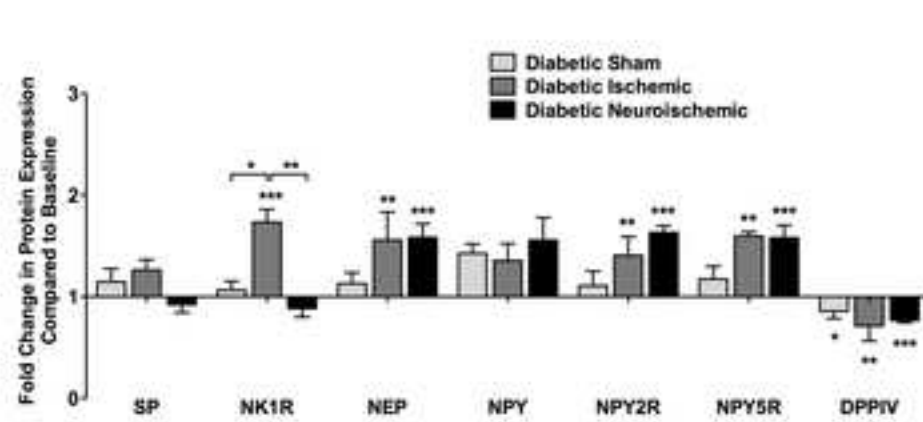
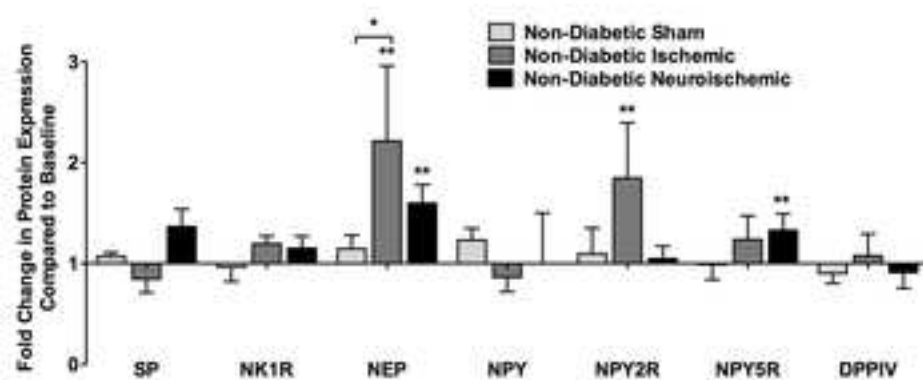
S10B



S11A



S11B



SUPPLEMENTARY TABLE LEGENDS:

Table S1: Weight and blood glucose data: Weight (Kg) and Fasting Blood Glucose (mg/dL) were obtained before alloxan administration (D0), on day of surgery (D10) and on day of euthanasia (D20). Results with significant changes are highlighted in the diabetic group. (N=6-18, mean±SEM, ***P<0.001).

Table S2: Wound healing numerical data: Data is presented as % of original wound size (Mean ± SEM). Comparisons are made between non-diabetic and diabetic groups. Results with significant changes are highlighted in the diabetic group. (N=6-18, mean±SEM, ***P<0.001 & *P<0.05).

Table S3: Leukocyte Infiltration data: Data is presented as the score of extent and intensity of infiltration (Mean ± SEM). Comparisons are made between non-diabetic and diabetic groups. Results with significant changes are highlighted in the diabetic group. (N=5-6, mean±SEM, ***P<0.001, **P<0.01 & **P<0.01).

Table S4: M1/M2 macrophage ratio: Comparisons are made between non-diabetic and diabetic groups. Results with significant changes are highlighted in the diabetic group. (N=3-4, mean±SEM, ***P<0.001, **P<0.01).

Table S5: Gene expression numerical data: Data is presented as relative gene expression (Mean ± SEM). Comparisons are made between non-diabetic and diabetic groups. Results with significant changes are highlighted in the diabetic group. (N=6-15, mean±SEM, ***P<0.001, **P<0.01, *P<0.05).

Table S6: Protein expression numerical data: Data is presented as relative protein expression (Mean \pm SEM). Comparisons are made between non-diabetic and diabetic groups. Results with significant changes are highlighted in the diabetic group. (N=4-6, mean \pm SEM, *P<0.05).

Table S7: List of PCR Primers

Table S8: List of antibodies for Western Blot and Immunohistochemistry

SUPPLEMENTARY FIGURE LEGENDS

Fig.S1: Experimental set up and representative images of wounds:

A) This schematic depicts the protocol timeline, treatment and surgical groups and an illustration of the rabbit ears indicating Ischemic/Neuroischemic and Sham ear. In the Ischemic/Neuroischemic ear, solid lines depict the incision site where the central and the rostral arteries are ligated along with the central and rostral nerves. Dashed lines in the sham ear depict incision site where the central and rostral artery and nerve are dissected but left intact.

B) Wound-healing was monitored over 10-day period from D10-D20. Photographs were obtained on D12, D15 and D20 using Medical Hyperspectral Imaging camera. Representative images are from non-diabetic and diabetic treatment groups of Sham, Ischemic and Neuroischemic wounds obtained on D20

Fig.S2: Representative H&E images the wounds indicating leukocyte infiltration. Formalin fixed paraffin embedded H&E stained 6 μ m cross-sections were analyzed for leukocyte infiltration. Representative images close to the wound margin are from non-diabetic and diabetic treatment groups and at Baseline and, Sham, Ischemic and Neuroischemic wounds (Mag =10X & 40X). Arrows indicate staining for immune cells.

Fig.S3: Representative images of A) M1+ and, B) M2+ macrophage infiltration: OCT embedded 6 μ m tissue sections were stained for macrophage marker CD18 and, co-stained for M1 macrophage activation marker HLA-DR or M2 macrophage activation marker CD206. Representative images close to the wound margin are from non-diabetic and diabetic treatment groups at Baseline and, Sham, Ischemic and Neuroischemic wounds (Mag = 5X). Merged

images (yellow/orange) of HLA-DR+ (red) and CD18+ (green) M1 macrophages and merged images (yellow/orange) of CD206+ (red) and CD18+ (green) M2 macrophages were obtained using standard fluorescent microscopy.

Fig.S4: Representative image of western blot analysis: Representative western blot of CXCR1, NK1R, NPY2R, NPY5R, NEP and DPPIV. Beta actin was used as a loading control. Blots are from non-diabetic and diabetic treatment groups at Baseline (B) and, Sham (S), Ischemic (I) and Neuroischemic (NI) wounds.

Fig.S5: Representative immunohistochemistry images of A) IL-8 and, B) IL6. OCT embedded 6 μ m frozen cross-sections were fixed with acetone and stained with IL-8 primary antibody. Formalin fixed paraffin embedded 6 μ m cross-sections were stained IL-6 primary antibody. Representative images close to the wound margin are from non-diabetic and diabetic treatment groups at Baseline and, Sham, Ischemic and Neuroischemic wounds (Mag=40X). Arrows indicate staining for IL-8 or IL-6.

Fig.S6: Representative immunohistochemistry images of A) Substance P (SP) and, B) Neuropeptide Y (NPY). Paraffin embedded 6 μ m cross-sections were stained with SP or NPY primary antibody. Representative images close to the wound margin are from non-diabetic and diabetic.

Fig.S7: Wound Healing: Comparison between wound types (sham, ischemic and neuroischemic) within non-diabetic and diabetic treatment groups: Data is expressed as

percent change in wound area pixels of non-diabetic and diabetic rabbits from days 2 to 10 (n=6-12, ***P<0.001).

Fig.S8: Leukocyte Infiltration: Comparison between wound types (sham, ischemic and neuroischemic) within non-diabetic and diabetic treatment groups: H&E stained cross-sections were analyzed for leukocyte infiltration. An arbitrary scale of 1-5 was used for grading entire cross-sections. Grading was performed on the basis of extent of infiltration (distance the cells migrated from the wound margin) and intensity of infiltration (# of infiltrating cells). Data are presented in the form of arbitrary scores. (N=5-6, mean±SEM, ***P<0.001 & **P<0.01).

Fig.S9: Macrophage Infiltration (M1/M2 ratio): Comparison between wound types (sham, ischemic and neuroischemic) within non-diabetic and diabetic treatment groups: Tissues were stained for M1 specific and M2 specific macrophages as described before. An arbitrary scale of 1-5 was used for grading cross-section images. M1/M2 ratio was obtained based on arbitrary scores. (N=3-4, mean±SEM, ***P<0.001, **P<0.01).

Fig.S10: Cytokines and Their Receptor: Post-injury comparison in the expression of IL-8, CXCR1 and IL-6 between wound types (sham, ischemic, neuroischemic) within non-diabetic and diabetic treatment groups:

A) Gene Expression: Using standard Q-RT-PCR and $2^{-\Delta\Delta Ct}$ analysis method, gene expression was analyzed. Data are expressed as change of expression over the baseline in non-diabetic and diabetic rabbit wounds (n=5-6, ***P<0.001, **P<0.01, P<0.05).

B) Protein Expression: Using standard western blot and immunohistochemistry methods, protein expression was analyzed. For western blot quantification, densitometry was used. For immunohistochemistry quantification, an arbitrary scale of 1-5 was used for grading entire cross-sections. Data expressed as change of expression over the baseline in non-diabetic and diabetic rabbit wounds (n=4-6, ***P<0.001, **P<0.01, P<0.05).

Fig.S11: Neuropeptide and Their Receptor: Post-injury comparison in the expression of SP, NK1R, NEP, NPY, NPY2R, NPY5R and DPPIV between wound types (sham, ischemic, neuroischemic) within non-diabetic and diabetic treatment groups:

A) Gene Expression: Using standard Q-RT-PCR and $2^{-\Delta\Delta Ct}$ analysis method, gene expression was analyzed. Data are expressed as change of expression over the baseline in non-diabetic and diabetic rabbit wounds (n=5-6, ***P<0.001, **P<0.01, P<0.05).

B) Protein Expression: Using standard western blot and immunohistochemistry methods, protein expression was analyzed. For western blot quantification, densitometry was used. For immunohistochemistry quantification, an arbitrary scale of 1-5 was used for grading entire cross-sections. Data expressed as change of expression over the baseline in non-diabetic and diabetic rabbit wounds (n=4-6, ***P<0.001, **P<0.01, P<0.05).