Supporting Information

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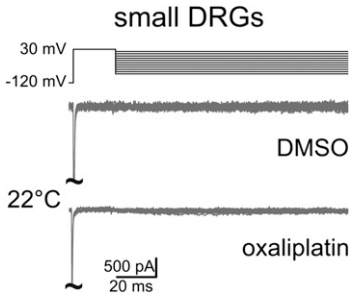

Fig. S1. Mediate persistent (I_{NaP}) and resurgent currents (I_{NaR}) are not apparent in small diameter dorsal root ganglion (DRG) neurons and are not affected by oxaliplatin. Representative whole-cell currents in response to a series of voltage commands (*Upper*) from small diameter (20.3 + 0.8 μm, *n* = 12) DRG neurons from wild-type mice after incubation with vehicle or oxaliplatin (30 μM, ~90 min). Neither tetrodotoxin-sensitive (TTX-s) I_{NaR} nor I_{NaP} were observed in any of the 12 neurons following vehicle or oxaliplatin. Postnatal day (P) 14–25 mice were used.

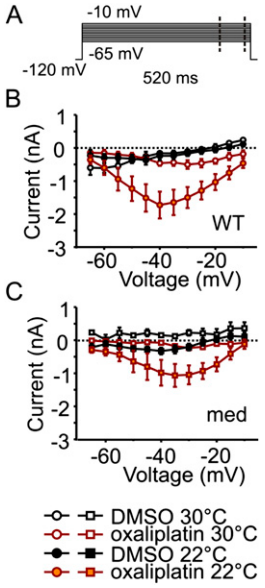

Fig. S2. Oxaliplatin (30 μM, 90 min) at 22 °C induces I_{NaP} in large DRG neurons. (*A*) Single-step voltage protocol to assess the voltage-dependence of persistent current. Persistent current was determined as the mean current over a 75-ms period between 420 and 495 ms indicated by the broken vertical lines. (*B*) Persistent current amplitude as a function of voltage for large-diameter DRGs from wild-type mice was larger in the presence of oxaliplatin at 22 °C. (*C*) Persistent current amplitude as a function of voltage for large-diameter DRGs from *Scn8a*$^{med/med}$ mice were similarly larger in the presence of oxaliplatin at 22 °C, but not as prominently as in DRG neurons from wild-type mice (*n* = 5–15, P14–P25).

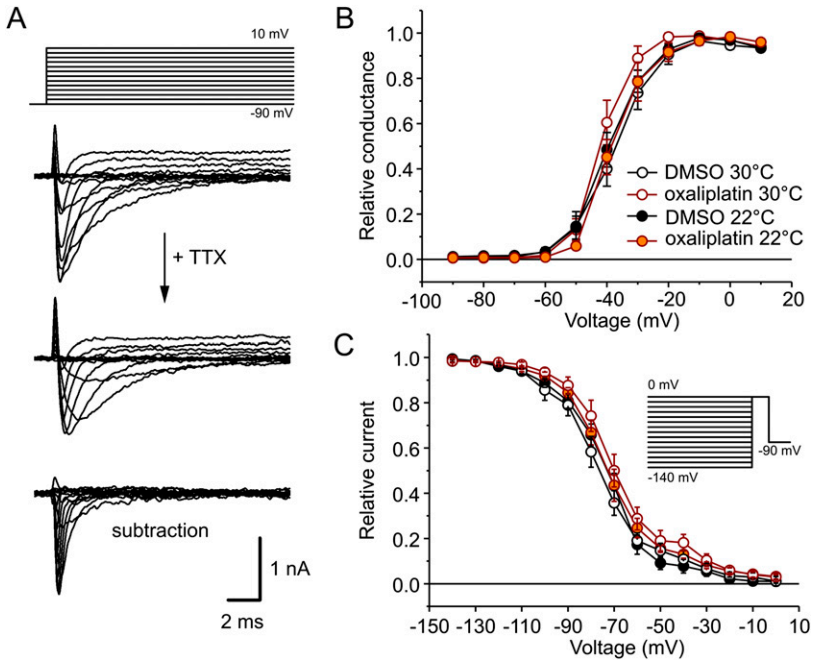

Fig. S3. Activation and steady-state fast inactivation of TTX-s sodium currents in large diameter DRGs are not affected by oxaliplatin (30 μM, 90 min). (*A* and *B*) To assess sodium current activation, large-diameter DRG neurons from wild-type mice were held at −90 mV and depolarized in 10-mV increments up to +10 mV. To improve voltage clamp, external sodium was reduced to 10 mM (see current traces in *A*) . Conductances were determined as detailed in *Materials and Methods* and normalized to the maximum conductance. (*C*) Steady-state fast inactivation was assessed using a brief test pulse to +0 mV applied at the end of a 500-ms prepulse at voltages between −140 and +0 mV (*C*, *Inset*). Peak inward current was normalized to the maximum current.

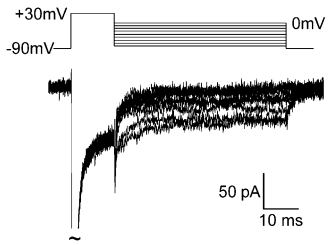

Fig. S4. Resurgent current was not observed in ND7 cells cotransfected with mNav1.6r and β4-subunit and exposed to oxaliplatin. Representative current recordings from one of 11 ND7 cells cotransfected with mNav1.6r and β4-subunit following incubation with oxaliplatin (30 μM, 90 min).

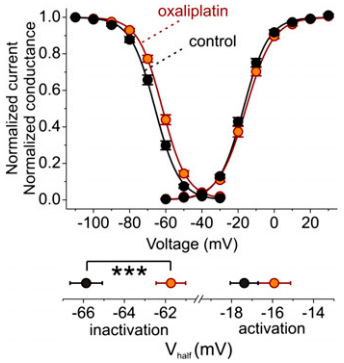

Fig. S5. Oxaliplatin produces a depolarizing shift of steady-state fast inactivation for mNav1.6r cotransfected with β4 subunit in ND7 cells. Voltage-dependence of activation (g–V curve) and steady-state fast inactivation (control: black symbols, n = 31; oxaliplatin 30 μM: gray markers, n = 25) in ND7 cells cotransfected with mNav1.6r and β4 subunit. Activation was assessed using the step protocol shown in in Fig. 5*C*, *Inset*. Conductance was calculated as outlined in *Materials and Methods*. A 1-s prepulse followed by a test pulse to 0 mV was used to assess steady-state fast inactivation. Recordings were performed at room temperature (~22 °C). (***$P < 0.001$).

Table S1. Repetitive activity in single axons in mouse saphenous nerve during cooling following exposure to oxaliplatin (100 μM, 90 min)

Genotype	Parameter	Aβ-fibers	Aδ-fibers	C-fibers
Control (*Scn8a*$^{+/+}$ and *Scn8a*$^{+/med}$)	*fibers showing repetitive activty/total fibers*	7/7	13/13	0/16
	Conduction velocity (m/s)	8.7 ± 0.9	4.0 ± 1.7	0.7 ± 0.4
Scn8a$^{med/med}$	*fibers showing repetitive activty/total fibers*	0	0/6	0/9
	Conduction velocity (m/s)	0	3.8 ± 0.6	0.7 ± 0.4

Fiber classification by conduction velocity (m/s): Aβ ≥ 7; 7 > Aδ > 2; C ≤ 2. Data from 32 mice; age: 14–141 d (34.5 ± 35.5 d); weight: 3.0–30.4 g (13.1 ± 8.5 g). For *Scn8a*^{med} mice that die around P20, axons with Aβ conduction velocities are not present.

Table S2. Mouse sural nerve excitability parameters before (control) and after oxaliplatin (100 μM, 90 min)

Parameter or threshold	Parameter	Control	Oxaliplatin	*P* value
Parameters sensitive to membrane potential	Current to evoke 50% max. CAP (μA)	2.9 ± 0.4	2.9 ± 0.5	0.59
	Rheobase current (μA)	1.6 ± 0.3	1.7 ± 0.3	0.27
	Strength-duration time constant (μs)	315.8 ± 50.2	299.6 ± 38.7	0.26
	Superexcitability at 7 ms (%)	2.8 ± 2.6	3.6 ± 2.6	0.77
TE d- depolarizing h- hyperpolarizing	TEd 10–20ms (%)	39.8 ± 2.8	46.3 ± 2.4	<0.01
	TEd 90–100ms (%)	31.6 ± 2.6	40.0 ± 2.8	<0.01
	TEh 20–40ms (%)	−78.5 ± 10.0	−79.6 ± 10.9	0.41
	TEh 90–100ms (%)	−86.4 ± 12.6	−85.7 ± 13.4	0.63

Threshold electrotonus (TE) parameters were determined using polarizing currents set to ± 40% of the unconditioned threshold. Values presented as mean ± SEM, *n* = 9; age: 122–194 d (163.8 ± 63.9 d); weight: 24.4–34.0 g (27.9 ± 3.1 g). Recording temperature: 25.5 ± 1 °C. CAP, compound action potential.

Table S3. Results from Boltzmann fits to the voltage-dependence of activation and steady-state fast inactivation of TTX-s sodium currents in large diameter DRG neurons

		Activation			Steady-state fast inactivation		
Temperature	Condition	V_{half} (mV)	Slope	*n*	V_{half} (mV)	Slope	*n*
30 °C	DMSO	−37.2 ± 2.7	5.7 ± 0.5	10	−77.5 ± 2.5	9.6 ± 0.8	10
	Oxaliplatin (30 μM)	−41.3 ± 1.7	4.6 ± 0.9	4	−70.2 ± 3.4	8.5 ± 0.7	6
22 °C	DMSO	−39.0 ± 1.9	5.2 ± 0.5	12	−73.8 ± 2.5	9.8 ± 0.8	11
	Oxaliplatin (30 μM)	−37.5 ± 2.1	5.2 ± 0.8	5	−73.0 ± 2.6	9.6 ± 1.3	6

ANOVA revealed no statistically significant differences between or within temperature and treatment.