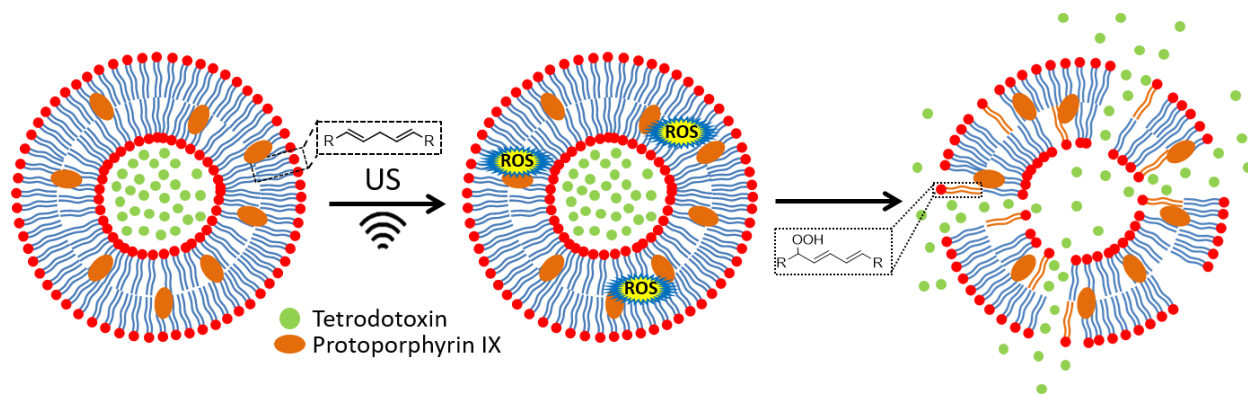


## Table of Contents

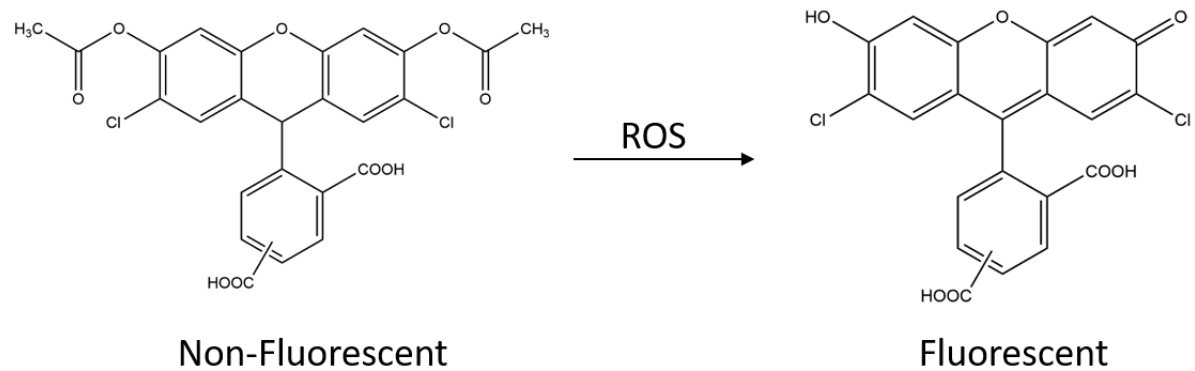
Scheme S1. Schematic of ultrasound-triggered liposomal drug release. ....	4
Scheme S2. Schematic of ROS indicator Carboxy-H2DCFDA and its mechanism of detection. ....	5
Figure S1. Particle size of Lipo-PPIX before and after ultrasound exposure determined by dynamic light scattering. ....	6
Figure S2. Dye release from irradiation of SRho-loaded liposomes with 400 nm light at 5 mW/cm <sup>2</sup> for 10 min. ....	7
Figure S3. TTX concentration of Lipo-PPIX-TTX before and after insonation. ....	8
Figure S4. Pharmacokinetics of SRho after insonation (at time 0) of Lipo-PPIX-SRho and Lipo-SRho. ...	9
Figure S5. Thermal latency measurement in animals injected at the sciatic nerve with Lipo-PPIX. ....	10
Figure S6. Thermal latency measurement after insonation at time 0. ....	11
Figure S7. DSPC-TTX liposomes (Lipo-DSPC-TTX). ....	12
Figure S8. Representative cryo-TEM micrograph of Lipo-DMED. ....	13
Figure S9. Representative thermal latency measurements from one out of four animals injected with free drug TTX and DMED. ....	14
Figure S10. Representative photograph of tissue dissection of animals co-injected with Lipo-PPIX-TTX + Lipo-DMED, 4 d after the last insonation. ....	15
Figure S11. Representative photomicrographs of hematoxylin & eosin-stained sections of injection sites 4 d after the last ultrasound event. ....	16
Figure S12. Representative photomicrographs of hematoxylin & eosin-stained sections from tissues exposed to ultrasound and harvested the same day. ....	17
Figure S13. Representative photomicrographs of sciatic nerve sections harvested 4 d after the last ultrasound event and stained with toluidine blue. ....	18
Figure S14. <i>In vitro</i> ultrasonography of Lipo taken with a 40-MHz ultrasound transducer. ....	19
Figure S15. The setup for ultrasound-guided injections. ....	20
Figure S16. <i>In vitro</i> ultrasonography of Lipo-PPIX taken with a 20-MHz ultrasound transducer. ....	21
Table S1. Characterization of liposomes ....	22
Table S2. Duration of nerve block after administration and repeated insonation. ....	23
Table S3. Duration of nerve block from co-administration of Lipo-PPIX-TTX + Lipo-DMED and after subsequent application of ultrasound with varying durations. ....	24
Table S4. Nerve block duration and peak thermal latency from co-administration of Lipo-PPIX-TTX + Lipo-DMED and after subsequent application of ultrasound with varying intensities. ....	25
Table S5. Tissue reaction 4 days after injections. ....	26
Table S6. Individual data points for Figure 1a. ....	27
Table S7. Individual data points for Figure 1b ....	27
Table S8. Individual data points for Figure 1c. ....	27
Table S9. Individual data points for Figure 1d ....	29

Table S10. Individual data points for Figure 1e.....	29
Table S11. Individual data points for Figure 1f.....	30
Table S12. Individual data points for Figure 2a, US group .....	30
Table S13. Individual data points for Figure 2a, no US group .....	30
Table S14. Individual data points for Figure 2b .....	31
Table S15. Individual data points for Figure 3b .....	31
Table S16. Individual data points for Figure 3c.....	32
Table S17. Individual data points for Figure 4a.....	33
Table S18. Individual data points for Figure 4b .....	34
Table S19. Individual data points for Figure 5a.....	35
Table S20. Individual data points for Figure 5b .....	38
Table S21. Individual data points for Figure 5c.....	39
Table S22. Individual data points for Figure 5d .....	40



Scheme S1. Schematic of ultrasound-triggered liposomal drug release.

Sonosensitizer protoporphyrin IX (PPIX) was encapsulated within liposomes composed of lipids sensitive to reactive oxygen species (ROS). Upon insonation, ROS generated by the sonosensitizers would react with the lipid bilayer and induce drug release.



Scheme S2. Schematic of ROS indicator Carboxy-H2DCFDA and its mechanism of detection.

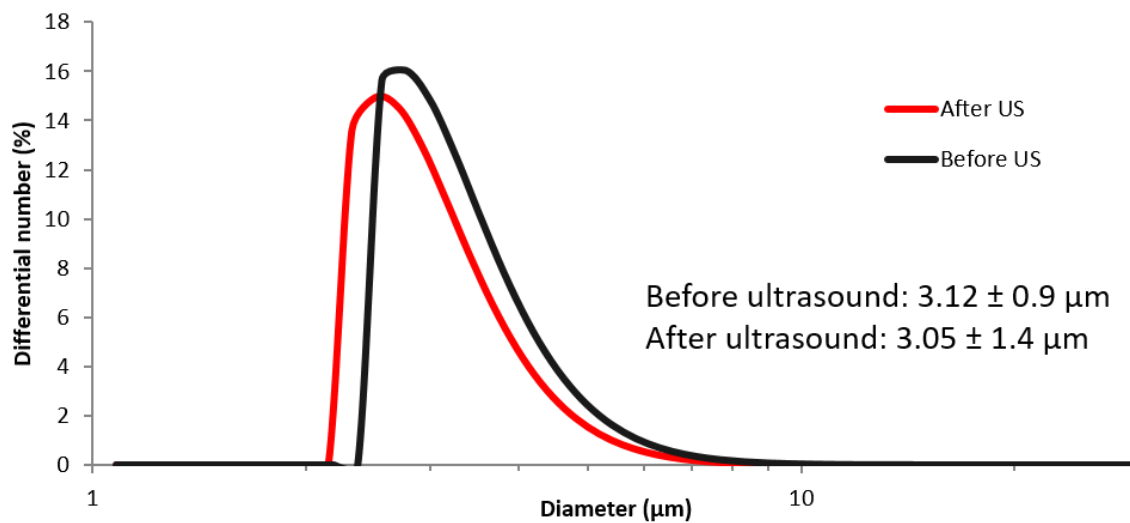


Figure S1. Particle size of Lipo-PPIX before and after ultrasound exposure ( $3 \text{ W/cm}^2$ , 1 MHz, 10 min) determined by dynamic light scattering. P=0.95, N=4.

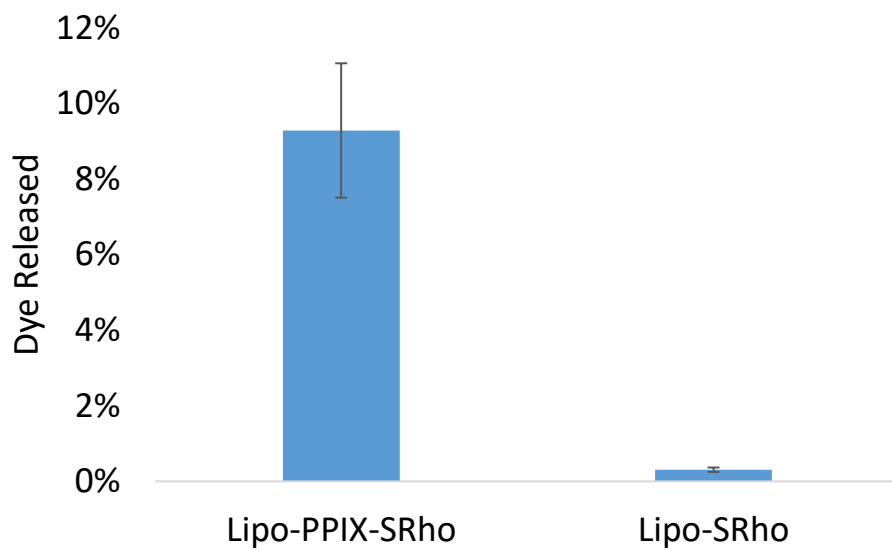


Figure S2. Dye release from irradiation of SRho-loaded liposomes with 400 nm light at 5 mW/cm<sup>2</sup> for 10 min.

P < 0.01 in comparison of the two groups, N=4.

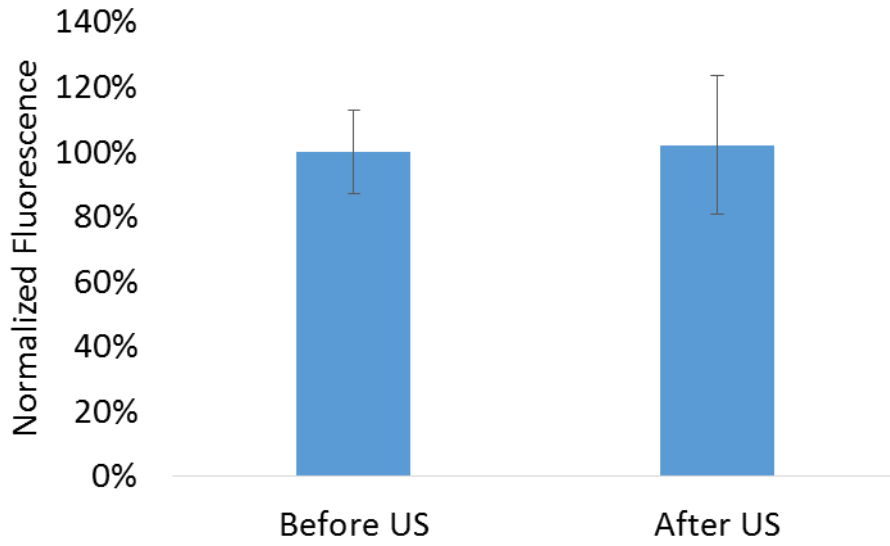


Figure S3. TTX concentration of Lipo-PPIX-TTX before and after insonation (3 W/cm<sup>2</sup>, 1 MHz, 10 min). The fluorescence before insonation (Before US) was normalized to 100%. P = 0.43 for comparison of the two groups, N=4.

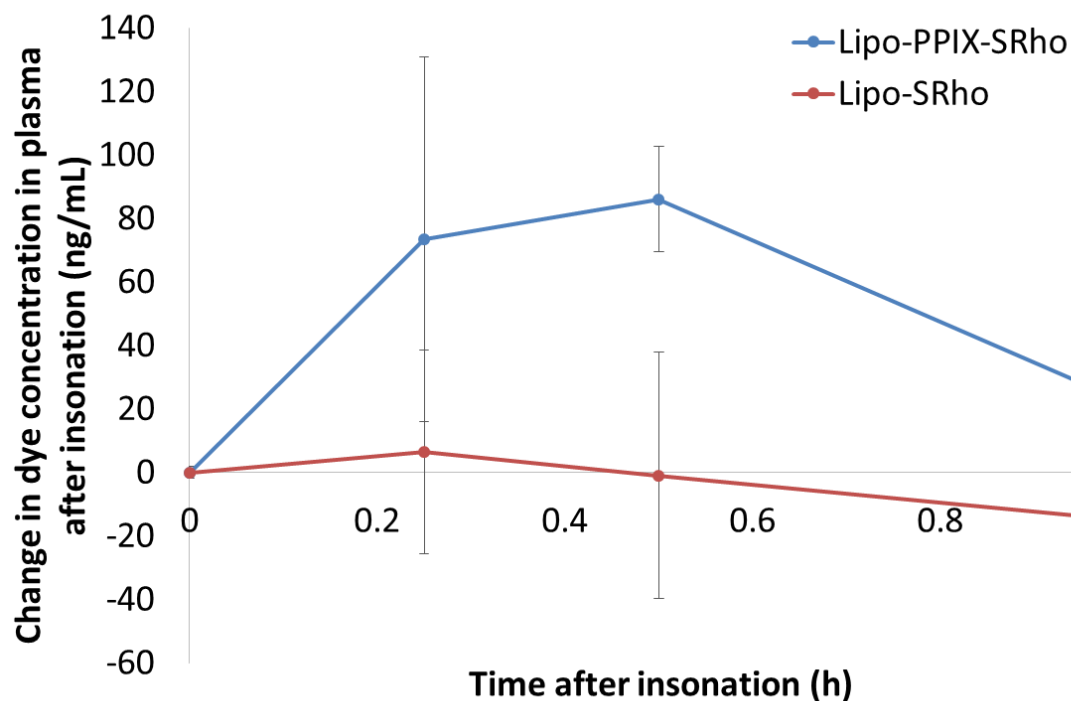


Figure S4. Pharmacokinetics of SRho after insonation (at time 0) of Lipo-PPIX-SRho and Lipo-SRho.

Animals were injected with liposomal formulations at the rat sciatic nerve with equivalent dosages of 1.5 mg/kg SRho. SRho was used as a proxy for TTX because both are very hydrophilic. (Modeling with ChemDraw software showed that TTX has a CLogP [calculated LogP] of -3.87, and SRho has a CLogP of -3.38.) Insonation was performed on all animals 22 h after injection. Blood was collected from the tail at the pre-determined time points and the concentration of SRho in the blood was measured. Animals injected with Lipo-PPIX-SRho showed a rapid increase in the plasma SRho concentration, while those injected with Lipo-SRho did not.  $P = 0.03$  at 0.5 h after insonation,  $N=3$ .



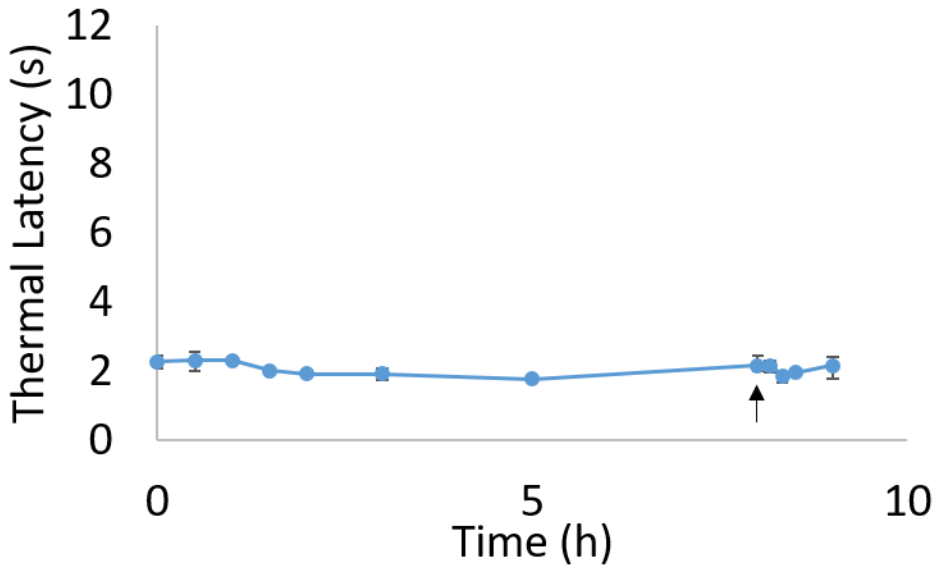


Figure S5. Thermal latency measurement in animals injected at the sciatic nerve with Lipo-PPIX at time 0.

Ultrasound was applied 8h after injection (1 MHz, 3 W/cm<sup>2</sup>, 10 min). N=4.

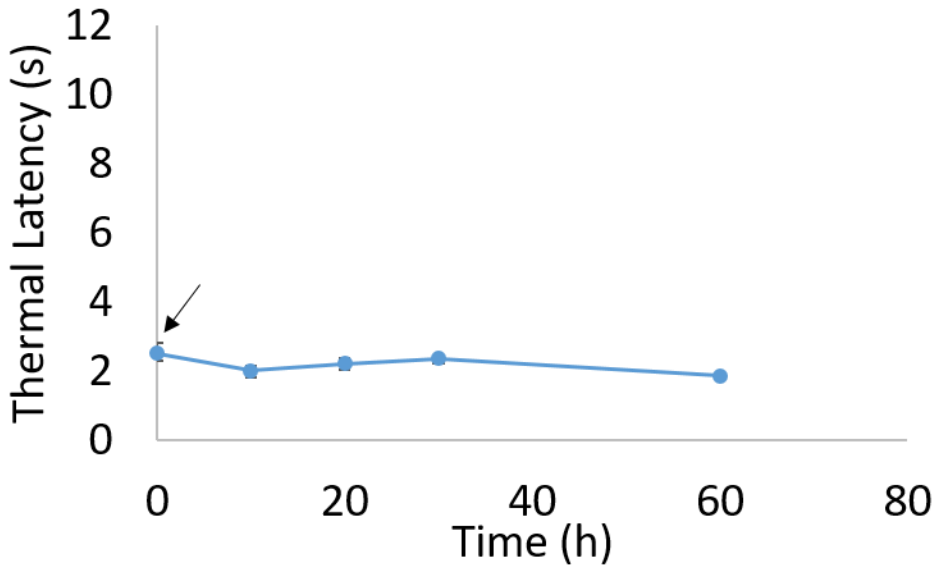


Figure S6. Thermal latency measurement after insonation at time 0. Ultrasound conditions were: 1 MHz, 3 W/cm<sup>2</sup>, 10 min. N=4.

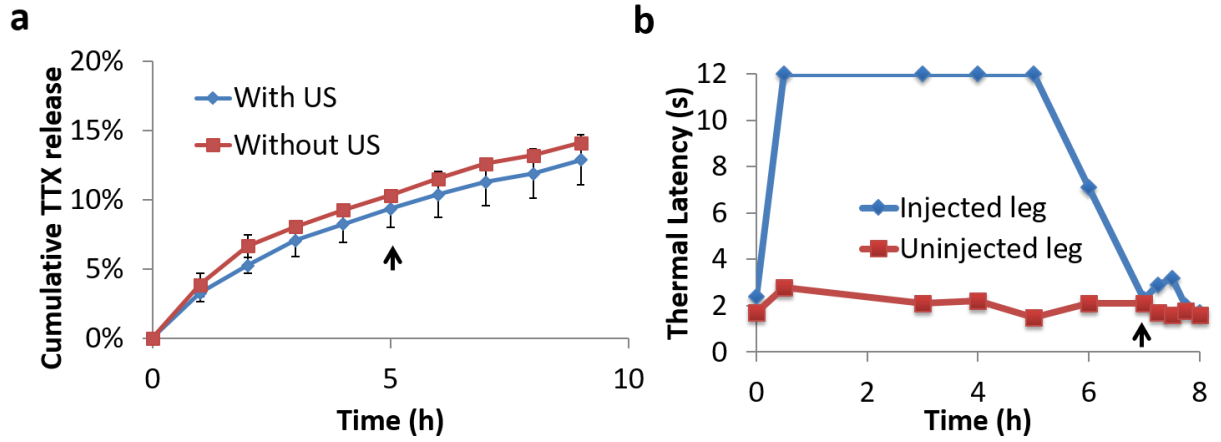


Figure S7. DSPC-TTX liposomes (Lipo-DSPC-TTX).

(a) In vitro TTX release.  $P=0.11$  at 9 h time point,  $N=4$ . (b) In vivo sciatic nerve block.

Insonation was performed after the thermal latency of the injected leg decreased to  $< 4$  s.

Insonation did not induce nerve block in any animals,  $N=4$ . Black arrows indicate insonation at  $3 \text{ W/cm}^2$ , 1 MHz for 10 min.

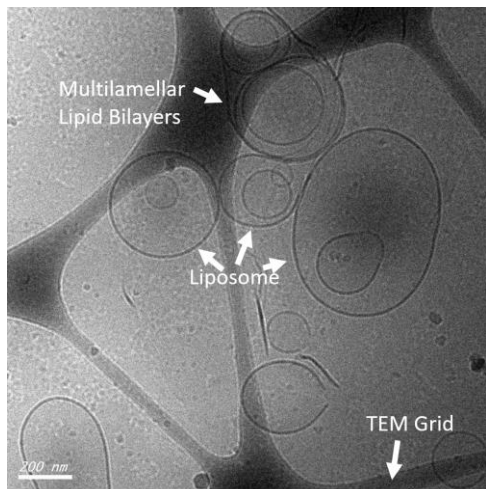


Figure S8. Representative cryo-TEM micrograph of Lipo-DMED. The scale bar is 200 nm.

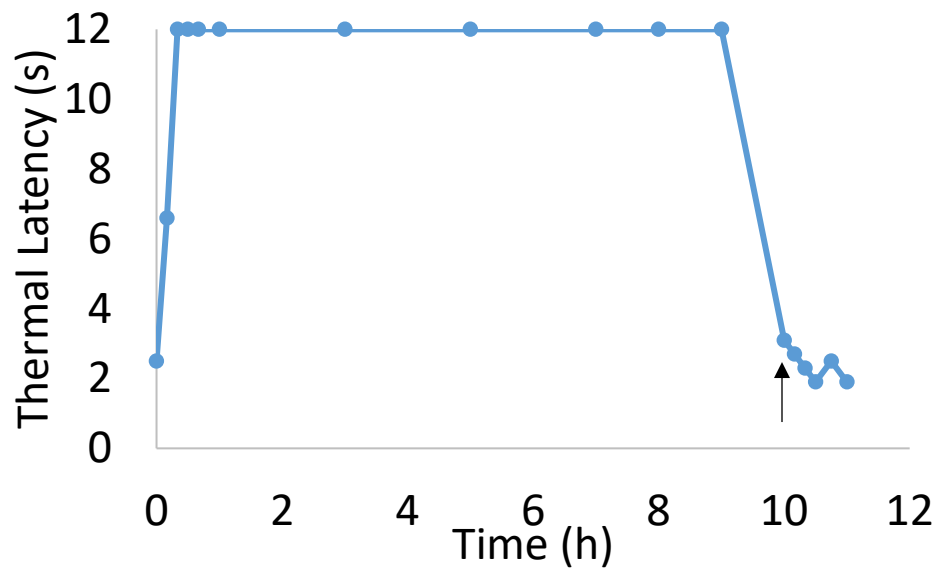


Figure S9. Representative thermal latency measurements from one out of four animals injected with free drug TTX and DMED.

Animals were injected with 0.3 mL of solution that had a TTX concentration of 0.02 mM and a DMED concentration of 0.07 mM. Ultrasound was applied (arrow) after the thermal latency returned below 4 s.

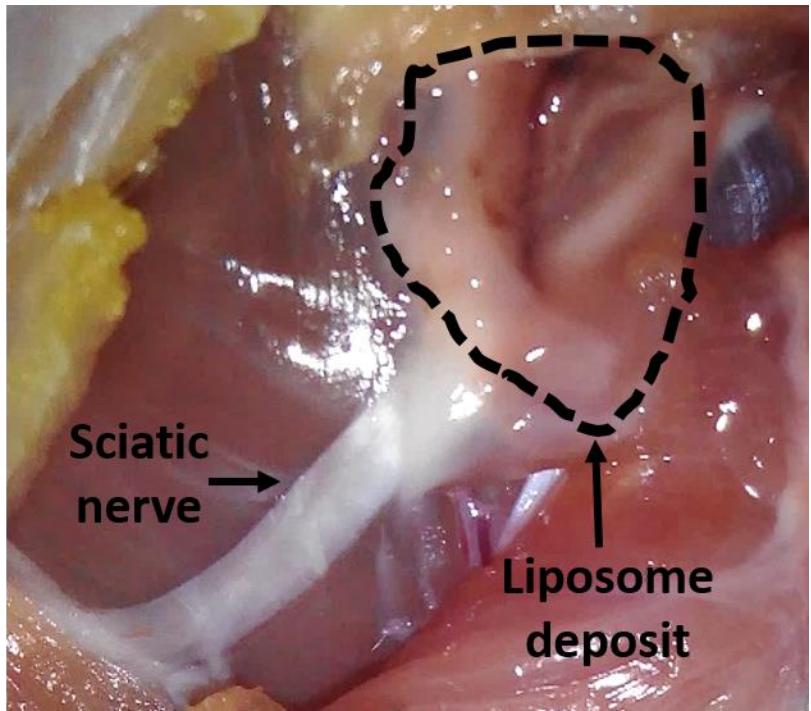


Figure S10. Representative photograph of tissue dissection of animals co-injected with Lipo-PPIX-TTX + Lipo-DMED, 4 d after the last insonation. Reddish-brown liposomes were observed to be in proximity with the sciatic nerve.

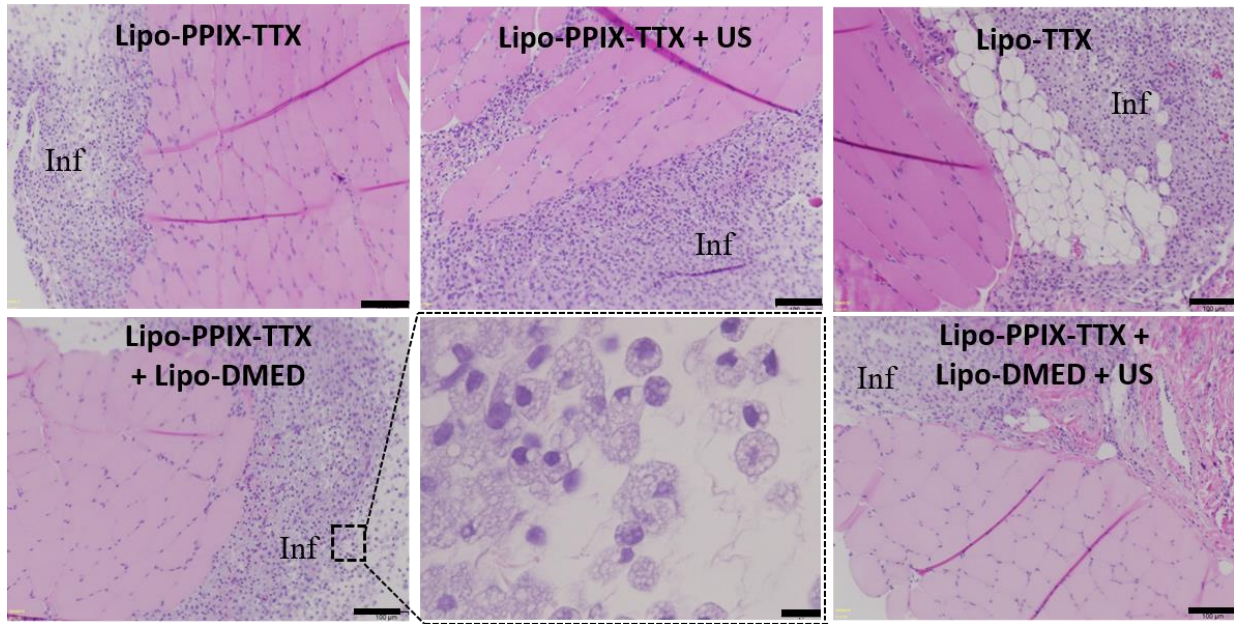


Figure S11. Representative photomicrographs of hematoxylin & eosin-stained sections of injection sites 4 d after the last ultrasound event.

High magnification of the inflammation is provided in one group, demonstrating the foamy appearance of the macrophages. Scale bars are 100  $\mu\text{m}$  for low magnification and 10  $\mu\text{m}$  for high magnification. Inf: inflammation.

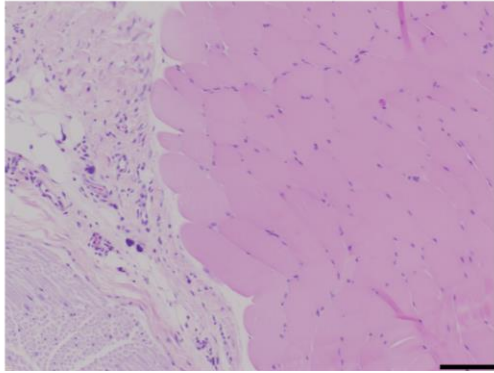
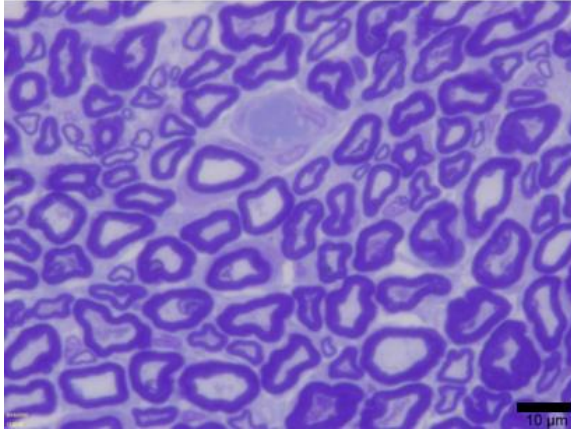


Figure S12. Representative photomicrographs of hematoxylin & eosin-stained sections from tissues exposed to ultrasound and harvested the same day.  
Scale bar = 100  $\mu\text{m}$ .



**Lipo-PPIX-TTX + US**



**Lipo-PPIX-TTX + Lipo-DMED + US**

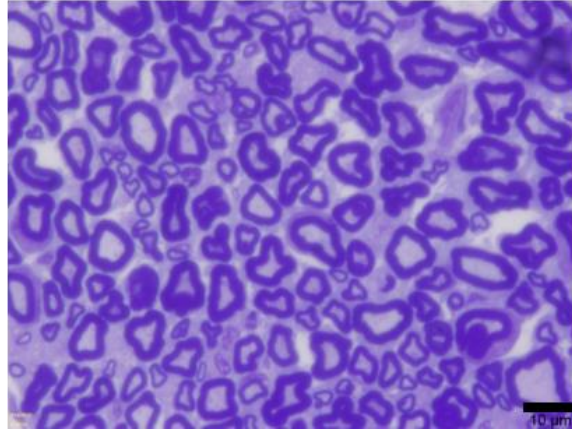


Figure S13. Representative photomicrographs of sciatic nerve sections harvested 4 d after the last ultrasound event and stained with toluidine blue. Scale bars are 10  $\mu\text{m}$ .

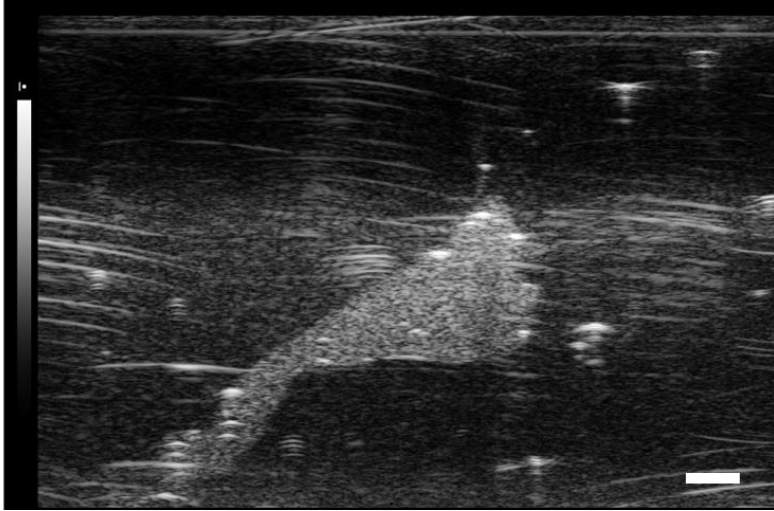


Figure S14. *In vitro* ultrasonography of Lipo taken with a 40-MHz ultrasound transducer. Scale bar = 1 mm.

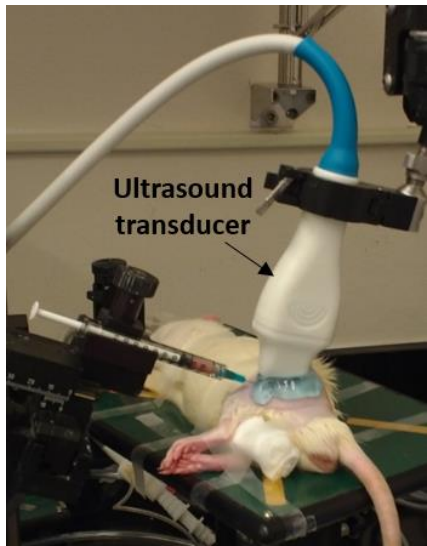


Figure S15. The setup for ultrasound-guided injections. Ultrasound-guided injections were performed with a 40-MHz ultrasound transducer. Ultrasound gel was applied between the transducer and the animal. Liposomes were injected with a 23G needle.

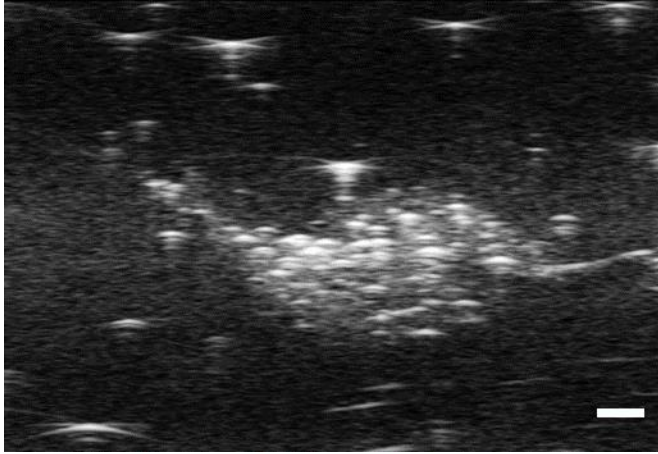


Figure S16. *In vitro* ultrasonography of Lipo-PPIX taken with a 20-MHz ultrasound transducer. Scale bar = 1 mm.

Table S1. Characterization of liposomes

	<u>Compound concentration</u>			<u>Loading efficiency (%)</u>		
	<b>PPIX (<math>\mu\text{g/mL}</math>)</b>	<b>SRho (<math>\text{mg/mL}</math>)</b>	<b>TTX (<math>\mu\text{g/mL}</math>)</b>	<b>PPIX</b>	<b>SRho</b>	<b>TTX</b>
<b>Lipo-PPIX-TTX</b>	197.7 $\pm$ 21.2	-----	83.3 $\pm$ 0.5	79.1 $\pm$ 8.5	-----	22.2 $\pm$ 0.2
<b>Lipo-TTX</b>	-----	-----	78.2 $\pm$ 7.4	-----	-----	20.9 $\pm$ 2.0
<b>Lipo-PPIX-Srho</b>	185.3 $\pm$ 27.3	2.6 $\pm$ 0.2	-----	74.1 $\pm$ 10.9	26.1 $\pm$ 1.8	-----
<b>Lipo-Srho</b>	-----	2.4 $\pm$ 0.2	-----	-----	23.9 $\pm$ 1.6	-----

Data are means  $\pm$  SD, N = 4.

Table S2. Duration of nerve block after administration and repeated insonation.

Injected liposomal formulation	Nerve block duration after treatment (h)				
	Injection	1st Insonation	2nd Insonation	3rd Insonation	4th Insonation
<b>Lipo-PPIX-TTX</b>	8.30 ± 4.70	0.66 ± 0.20	0.24 ± 0.17	0 ± 0	-----
<b>Lipo-PPIX-TTX +Lipo-DMED</b>	33.46 ± 5.04	1.77 ± 1.21	0.85 ± 0.34	0.48 ± 0.27	0 ± 0 *
<b>P values</b>	< 0.001	0.06	0.01	0.01	

\* Peak thermal latency between 4 s and 7 s after insonation, i.e. deficit in sensory testing but not enough to qualify as nerve block in our definition.

----- : Insonation not performed

Data are means ± SD, N = 4. Ultrasound (3 W/cm<sup>2</sup>, 1 MHz, 10 min) was applied after the previous nerve block returned to ≤ 4 s.

Table S3. Duration of nerve block from co-administration of Lipo-PPIX-TTX + Lipo-DMED and after subsequent application of ultrasound with varying durations

Insonation duration	Nerve block duration after treatment (h)						
	Injection	1st Insonation	2nd Insonation	3rd Insonation	4th Insonation	5th Insonation	6th Insonation
2 min	33.44 ± 3.67	0.19 ± 0.15	0 ± 0	-----	-----	-----	-----
5 min	27.01 ± 2.39	0.53 ± 0.24	0.38 ± 0.08	0.38 ± 0.10	0.28 ± 0.06	0.26 ± 0.12	0 ± 0 *
10 min	33.46 ± 5.04	1.77 ± 1.21	0.85 ± 0.34	0.48 ± 0.27	0 ± 0 *	-----	-----
<b>P value (2 min compared with 5 min)</b>	0.03	0.03	< 0.001				
<b>P value (5 min compared with 10 min)</b>	0.06	0.04	0.02	0.26	< 0.001		

\* Peak thermal latency between 4 s and 7 s after insonation, i.e. deficit in sensory testing but not enough to qualify as nerve block in our definition.

----- : Insonation not performed

Data are means ± SD, N = 4. Ultrasound (3 W/cm<sup>2</sup>, 1 MHz, 10 min) was applied after the previous nerve block returned to ≤ 4 s.

Table S4. Nerve block duration and peak thermal latency from co-administration of Lipo-PPIX-TTX + Lipo-DMED and after subsequent application of ultrasound with varying intensities

	<b>Ultrasound intensity (W/cm<sup>2</sup>)</b>			<b>P value: 1W/cm<sup>2</sup> vs 3W/cm<sup>2</sup></b>
	<b>1</b>	<b>2</b>	<b>3</b>	
<b>Nerve block duration (h)</b>	0.1 ± 0.1	0.7 ± 0.8	2.3 ± 0.8	< 0.001
<b>Peak thermal latency (s)</b>	6 ± 2.9	9.1 ± 4.3	12 ± 0	0.003

Data are means ± SD, N = 4.



Table S5. Tissue reaction 4 days after injections.

<b>Liposomal Formulation</b>	<b>Inflammation</b>	<b>Myotoxicity</b>
Lipo-PPIX-TTX	1(1-1)	0 (0-0)
Lipo-PPIX-TTX + US	1(1-1)	0 (0-0)
Lipo-TTX + US	1 (0.5-1)	0 (0-0.5)
Lipo-PPIX-TTX + Lipo-DMED + US	1(0.8-1)	0 (0-0)

Data are medians with interquartile ranges in parentheses. N = 4 for all groups except for Lipo-TTX (data are from 3 of 6 rats that survived). There were no statistically significant differences between groups for each score type.

Table S6. Individual data points for Figure 1a

Data are the fluorescence of solution as a measure of ROS generation.

	<b>Repeat 1</b>	<b>Repeat 2</b>	<b>Repeat 3</b>	<b>Repeat 4</b>
<b>Column 1 (no US)</b>	294	274	248	282
<b>Column 2 (no PPIX)</b>	362	331	376	392
<b>Column 3 (0.15% PPIX)</b>	387	457	366	401
<b>Column 4 (0.3% PPIX)</b>	535	566	655	418
<b>Column 5 (0.45% PPIX)</b>	348	406	510	682
<b>Column 6 (0.6% PPIX)</b>	361	604	339	487

Table S7. Individual data points for Figure 1b

Data are absorption at 569 nm for the measurement of lipid peroxidation.

	<b>Repeat 1</b>	<b>Repeat 2</b>	<b>Repeat 3</b>	<b>Repeat 4</b>
<b>0 min</b>	0.288	0.304	0.316	0.309
<b>10 min</b>	0.315	0.333	0.323	0.332
<b>15 min</b>	0.326	0.362	0.341	0.341
<b>20 min</b>	0.386	0.38	0.376	0.381

Table S8. Individual data points for Figure 1c

Data are dye release percentages from different liposome formulations.

	<b>Repeat 1</b>	<b>Repeat 2</b>	<b>Repeat 3</b>	<b>Repeat 4</b>
<b>Column 1 (DLPC, 0.3% PPIX, no US)</b>	0	0	0	0
<b>Column 2 (DSPC, 0.3% PPIX, with US)</b>	2.14	1.73	2.02	3.11
<b>Column 3 (DLPC, no PPIX, with US)</b>	3.64	4.45	4.77	4.12

<b>Column 4 (DLPC, 0.15% PPIX, with US)</b>	5.31	4.91	4.54	5.80
<b>Column 5 (DLPC, 0.3% PPIX, with US)</b>	10.32	11.02	12.35	13.51
<b>Column 6 (DLPC, 0.45% PPIX, with US)</b>	7.44	7.73	9.78	9.53
<b>Column 7 (DLPC, 0.6% PPIX, with US)</b>	7.76	7.85	7.28	7.19

Table S9. Individual data points for Figure 1d

Data are dye release percentages under different insonation frequencies.

	<b>1 MHz</b>	<b>3 MHz</b>
<b>5 min repeat 1</b>	5.27	3.24
<b>5 min repeat 2</b>	5.07	3.43
<b>5 min repeat 3</b>	5.49	3.35
<b>5 min repeat 4</b>	2.97	4.25
<b>10 min repeat 1</b>	10.32	10.42
<b>10 min repeat 2</b>	11.02	8.33
<b>10 min repeat 3</b>	12.35	5.92
<b>10 min repeat 4</b>	13.51	8.77
<b>15 min repeat 1</b>	17.12	11.83
<b>15 min repeat 2</b>	19.45	12.73
<b>15 min repeat 3</b>	21.27	11.23
<b>15 min repeat 4</b>	20.22	14.11

Table S10. Individual data points for Figure 1e

Data are dye release percentages under different insonation intensities.

	<b>Intensity (W/cm<sup>2</sup>)</b>			
	<b>0.5</b>	<b>1</b>	<b>2</b>	<b>3</b>
<b>Repeat 1</b>	0.19	4.08	7.45	11.32
<b>Repeat 2</b>	0.17	5.16	6.05	11.02
<b>Repeat 3</b>	0.38	2.88	5.61	12.35
<b>Repeat 4</b>	1.75	2.33	5.16	13.51

Table S11. Individual data points for Figure 1f  
Data are dye release percentages of different insonation duty cycles.

	Duty Cycle (%)		
	20	50	100
<b>Repeat 1</b>	2.06	8.62	11.32
<b>Repeat 2</b>	1.74	7.79	11.02
<b>Repeat 3</b>	2.54	4.35	12.35
<b>Repeat 4</b>	1.62	5.67	13.51

Table S12. Individual data points for Figure 2a, US group  
Data are cumulative dye release percentages from the ultrasound-triggered (US) group.

Condition	Samples	Time (min)									
		0	5	10	15	20	25	30	35	40	45
US	<b>Repeat 1</b>	0.0	4.6	5.4	9.0	9.7	19.3	20.6	24.3	26.5	26.6
	<b>Repeat 2</b>	0.0	3.6	4.0	8.8	9.7	21.0	22.2	25.5	27.0	27.7
	<b>Repeat 3</b>	0.0	4.0	4.5	8.8	10.2	16.8	17.5	21.1	23.4	23.3
	<b>Repeat 4</b>	0.0	3.5	4.2	8.1	9.7	18.2	19.0	24.3	26.3	26.8
	<b>Repeat 5</b>	0.0	5.7	5.6	9.6	10.2	17.4	18.0	21.5	24.0	24.3
	<b>Repeat 6</b>	0.0	4.5	5.0	11.2	12.3	17.9	18.7	22.7	25.0	25.6

Table S13. Individual data points for Figure 2a, no US group  
Data are cumulative dye release percentages from the non-ultrasound-triggered (no US) group.

Condition	Samples	Time (min)				
		0	10	20	30	45
No US	<b>Repeat 1</b>	0	0.6	1.0	1.1	1.2
	<b>Repeat 2</b>	0	1.2	0.8	0.6	1.1
	<b>Repeat 3</b>	0	1.0	0.1	1.4	0.8
	<b>Repeat 4</b>	0	0.2	0.4	0.4	0.6
	<b>Repeat 5</b>	0	0.6	1.4	0.6	1.3

Table S14. Individual data points for Figure 2b

Data are the average integrated epifluorescence after insonation, normalized by the average integrated epifluorescence before insonation

	<b>Repeat 1</b>	<b>Repeat 2</b>	<b>Repeat 3</b>	<b>Repeat 4</b>
<b>With insonation</b>	1.48	1.69	1.63	1.72
<b>Without insonation</b>	1.02	1.03	0.90	0.85

Table S15. Individual data points for Figure 3b

Data are cumulative dye release percentages from Lipo-PPIX-SRho with and without repeated insonation.

<b>Condition</b>	<b>Samples</b>	<b>Time (h)</b>								
		<b>0</b>	<b>1*</b>	<b>2</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>
<b>No US</b>	<b>Repeat 1</b>	0.0	3.1	4.9	5.9	6.4	6.7	7.2	7.6	7.9
	<b>Repeat 2</b>	0.0	4.5	6.2	7.7	8.3	8.6	9.0	9.3	9.7
	<b>Repeat 3</b>	0.0	4.8	6.6	8.2	8.7	9.0	9.4	9.8	10.0
	<b>Repeat 4</b>	0.0	3.1	5.4	6.7	7.2	7.7	8.0	8.5	8.7
<b>US</b>	<b>Repeat 1</b>	0.0	3.1	5.0	6.6	7.3	8.8	10.0	10.8	11.3
	<b>Repeat 2</b>	0.0	4.5	6.5	8.1	8.7	10.5	11.7	12.5	12.9
	<b>Repeat 3</b>	0.0	4.8	7.3	9.3	9.9	12.2	13.5	14.2	14.9
	<b>Repeat 4</b>	0.0	3.1	7.0	8.6	9.1	13.0	15.3	16.5	17.3

\* Same data used for the "No US" and "US" groups, justified by the fact that they were under exact same conditions at the 1 h time point

Table S16. Individual data points for Figure 3c

Data are cumulative dye release percentages from Lipo-SRho with and without repeated insonation.

Condition	Samples	Time (h)									
		0	1*	2	3	4	5	6	7	8	9
No US	Repeat 1	0.0	9.2	13.8	17.0	18.4	19.5	20.2	21.0	21.7	22.2
	Repeat 2	0.0	9.7	15.2	18.5	20.2	21.3	22.7	23.7	24.8	25.4
	Repeat 3	0.0	5.0	8.9	11.1	13.0	14.3	15.5	16.4	17.4	18.1
	Repeat 4	0.0	15.3	22.0	25.0	26.7	27.9	28.9	30.0	31.0	31.6
US	Repeat 1	0.0	9.2	19.4	21.8	23.5	24.4	25.4	26.5	27.4	28.0
	Repeat 2	0.0	9.7	13.3	14.7	15.6	16.4	17.3	18.1	19.0	20.9
	Repeat 3	0.0	5.0	9.7	11.8	12.6	13.3	14.2	14.6	15.1	15.6
	Repeat 4	0.0	15.3	22.2	24.4	25.3	25.9	26.8	27.2	27.6	28.0

\* Same data used for the "No US" and "US" groups, justified by the fact that they were under exact same conditions at the 1 h time point

Table S17. Individual data points for Figure 4a  
 Data are thermal latencies after injection of Lipo-PPIX-TTX

Time after injection (h)	Rat 1 Thermal Latency (s)	Time after injection (h)	Rat 2 Thermal Latency (s)	Time after injection (h)	Rat 3 Thermal Latency (s)	Time after injection (h)	Rat 4 Thermal Latency (s)
0.5	4.9	0.5	5.2	0.5	4.9	0.5	5.5
3.0	12.0	3.0	10.2	3.0	12.0	3.0	12.0
5.0	12.0	4.0	5.5	5.0	7.6	5.0	12.0
7.0	12.0	5.0	3.3	6.0	4.8	7.0	12.0
9.0	12.0	6.0	2.6	7.0	3.2	9.0	9.7
11.0	12.0	Insonation		8.0	2.2	10.0	7.8
13.0	11.0	6.2	12.0	Insonation		11.0	4.0
14.0	6.2	6.3	11.2	8.2	9.0	12.0	4.0
15.0	3.8	6.5	7.8	8.3	7.6	13.0	3.1
16.0	1.8	6.8	6.2	8.5	6.0	Insonation	
Insonation		7.0	3.6	8.8	4.1	13.2	12.0
16.2	11.3	Insonation		9.0	2.4	13.3	11.8
16.3	9.7	7.2	7.5	Insonation		13.5	11.7
16.5	8.7	7.3	7.4	9.2	5.2	13.8	7.0
16.8	9.2	7.5	4.4	9.3	4.3	14.0	5.8
17.0	4.8	7.8	4.0	9.5	3.9	14.5	2.8
17.5	2.9	8.0	3.2	9.8	3.2	Insonation	
Insonation		Insonation		10.0	2.4	14.7	10.4
17.7	11.8	8.3	5.8	Insonation		14.8	4.1
17.8	7.6	8.5	5.9	10.2	3.1	15.0	3.0
18.0	4.6			10.3	3.3	Insonation	
18.3	2.6			10.5	3.1	15.2	2.3
Insonation				15.3	2.0		
18.4	2.7			15.5	2.4		



18.6	2.2
18.8	2.2

Table S18. Individual data points for Figure 4b  
Data are thermal latencies after injection of Lipo-TTX

Time after insonation (h)	Rat 1 Thermal Latency (s)	Time after insonation (h)	Rat 2 Thermal Latency (s)	Time after insonation (h)	Rat 3 Thermal Latency (s)
0.5	12	0.5	2.9	0.5	12
3	12	3	12	3	12
5	12	5	7.8	5	12
7	12	6	5.8	7	12
9	12	7	3.5	9	12
12	12	8	2.3	12	12
14	12	Insonation		14	12
16	12	8.2	3.4	16	12
18	8.2	8.3	3	18	12
19	4.7	8.5	2.6	20	12
20	2.2			22	12
Insonation				24	12
20.2	2.9			26	12
20.3	2.1			28	6.7
20.5	2.5			29	3.6
				30	2.8
				Insonation	
				30.2	2.1
				30.3	3.1
				30.5	2.8

Table S19. Individual data points for Figure 5a

Data are thermal latencies after injection of Lipo-PPIX-TTX and Lipo-DMED

Time after injection (h)	Rat 1 Thermal Latency (s)	Time after injection (h)	Rat 2 Thermal Latency (s)	Time (h)	Rat 3 Thermal Latency (s)	Time (h)	Rat 4 Thermal Latency (s)
0.5	3.6	0.5	3.0	0.5	3.6	0.5	4.9
3.0	12.0	3.0	12.0	3.0	12.0	3.0	12.0
5.0	12.0	5.0	12.0	5.0	12.0	5.0	12.0
7.0	12.0	7.0	12.0	7.0	12.0	7.0	12.0
9.0	12.0	9.0	12.0	9.0	12.0	9.0	12.0
11.0	12.0	11.0	12.0	11.0	12.0	11.0	12.0
13.0	12.0	13.0	12.0	13.0	12.0	13.0	12.0
15.0	12.0	15.0	12.0	15.0	12.0	15.0	12.0
17.0	12.0	17.0	12.0	17.0	12.0	17.0	12.0
19.0	12.0	19.0	12.0	19.0	12.0	19.0	12.0
21.0	12.0	21.0	12.0	21.0	12.0	21.0	12.0
23.0	12.0	23.0	12.0	23.0	12.0	23.0	12.0
25.0	12.0	25.0	12.0	25.0	12.0	25.0	12.0
27.0	12.0	27.0	10.4	27.0	8.8	27.0	12.0
28.0	12.0	28.0	9.6	28.0	7.6	28.0	12.0
29.0	12.0	29.0	8.2	29.0	6.4	29.0	12.0
30.0	12.0	30.0	6.6	30.0	5.7	30.0	12.0
31.0	12.0	31.0	4.5	31.0	2.2	31.0	12.0
32.0	12.0	32.0	2.8	32.0	2.2	32.0	12.0
33.0	12.0	33.0	1.9	Insonation		33.0	12.0
34.0	12.0	Insonation		32.2	12.0	34.0	12.0
35.0	12.0	33.2	12.0	32.3	12.0	35.0	12.0
37.0	6.0	33.3	12.0	32.5	12.0	37.0	12.0
38.0	3.8	33.5	5.0	32.8	10.6	38.0	10.7

39.0	4.7	33.8	3.6	33.0	7.3	39.0	6.1
40.0	2.1	34.0	2.3	33.5	5.4	40.0	3.6
Insonation		Insonation		34.0	3.1	41.0	3.8
40.2	12.0	34.2	12.0	Insonation		Insonation	
40.3	12.0	34.3	7.9	34.2	10.4	41.2	12.0
40.5	11.3	34.5	8.0	34.3	7.8	41.3	12.0
40.8	12.0	35.0	7.1	34.5	7.1	41.5	12.0
41.0	11.1	35.3	5.0	34.8	6.0	41.8	12.0
41.5	9.8	35.5	2.7	35.0	3.1	42.0	12.0
42.0	9.3	Insonation		35.5	2.8	42.5	12.0
42.5	7.0	35.7	9.3	Insonation		43.0	10.5
43.0	4.9	35.8	8.7	35.7	7.0	43.5	9.5
43.5	2.1	36.0	6.3	35.8	5.0	44.0	7.4
Insonation		36.3	5.0	36.0	6.0	44.5	3.8
43.7	12.0	36.5	2.7	36.3	3.3	44.8	2.2
43.8	12.0	Insonation		36.5	2.2	Insonation	
44.0	8.7	36.7	5.4	Insonation		44.9	12.0
44.3	7.6	36.8	2.7	36.7	2.5	45.1	12.0
44.5	4.0	37.0	2.4	36.8	3.1	45.3	12.0
44.8	3.7			37.0	2.3	45.5	10.7
Insonation						46.0	8.8
44.9	11.1					46.5	6.1
45.1	9.1					47.0	4.9
45.3	7.7					47.3	4.0
45.5	5.2					Insonation	
45.8	2.3					47.4	12.0
Insonation						47.6	11.0
45.9	5.9					47.8	8.3

46.1	3.5
46.3	2.0

48.0	7.4
48.3	5.1
48.5	2.9
Insonation	
48.7	6.8
48.8	4.5
49.0	3.9

Table S20. Individual data points for Figure 5b

Data are thermal latencies after insonation of animals injected with Lipo-PPIX-TTX and Lipo-DMED

Time (h)	2 min				5 min				10 min			
	animal 1	animal 2	animal 3	animal 4	animal 1	animal 2	animal 3	animal 4	animal 1	animal 2	animal 3	animal 4
0.0	3	2.2	2.6	3.2	3.2	2.1	1.5	2	2.1	2.2	3.8	2.2
0.2	7.8	5.5	7.4	5.3	8.3	7.2	12	12	12	12	12	12
0.3	4.6	7.6	5.3	5.2	3.9	9.2	11.3	12	12	12	12	12
0.5	3.3	3.9	4	2.5	2.1	6.6	9	8.9	11.3	12	12	12
0.8					2	5.7	5.4	7.2	12	10.6	12	11.4
1.0					2	5.9	4	5.1	11.1	7.3	12	11.5
1.5									9.8	5.4	12	10
2.0									9.3	3.1	10.5	9.1
2.5									7	2	9.5	7.1
3.0									4.9	2	7.4	5
3.5									2.1	2	3.8	3.2

Table S21. Individual data points for Figure 5c

Data are thermal latencies after insonation of animals injected with Lipo-PPIX-TTX and Lipo-DMED

<b>Ultrasound Duration (min)</b>	<b>Duration of Block (h)</b>			
	<b>animal 1</b>	<b>animal 2</b>	<b>animal 3</b>	<b>animal 4</b>
<b>2</b>	0.2	0.4	0.2	0.0
<b>5</b>	0.2	0.5	0.6	0.8
<b>7.5</b>	0.9	0.8	1.1	1.6
<b>10</b>	2.5	1.1	3.1	2.5
<b>15</b>	1.0	3.1	2.7	2.0

Table S22. Individual data points for Figure 5d

Data are thermal latencies after insonation of animals injected with Lipo-PPIX-TTX and Lipo-DMED

Time (h)	1W/cm <sup>2</sup>				2W/cm <sup>2</sup>				3W/cm <sup>2</sup>			
	animal 1	animal 2	animal 3	animal 4	animal 1	animal 2	animal 3	animal 4	animal 1	animal 2	animal 3	animal 4
0.0	2.9	2.8	3.8	3.7	3.3	3.5	3.1	3	2.1	2.2	3.8	2.2
0.2	2.8	9.9	5.1	6.2	5.6	8.2	12	7.9	12	12	12	12
0.3	2.8	3.4	3.2	6.2	2.7	10.7	12	10.9	12	12	12	12
0.5	2.6	3	2.3	4.3	2.7	6	12	4.3	11.3	12	12	12
0.8					2.3	3.5	12	3.8	12	10.6	12	11.4
1.0									11.1	7.3	12	11.5
1.5									9.8	5.4	12	10
2.0									9.3	3.1	10.5	9.1
2.5									7	2	9.5	7.1
3.0									4.9	2	7.4	5
3.5									2.1	2	3.8	3.2