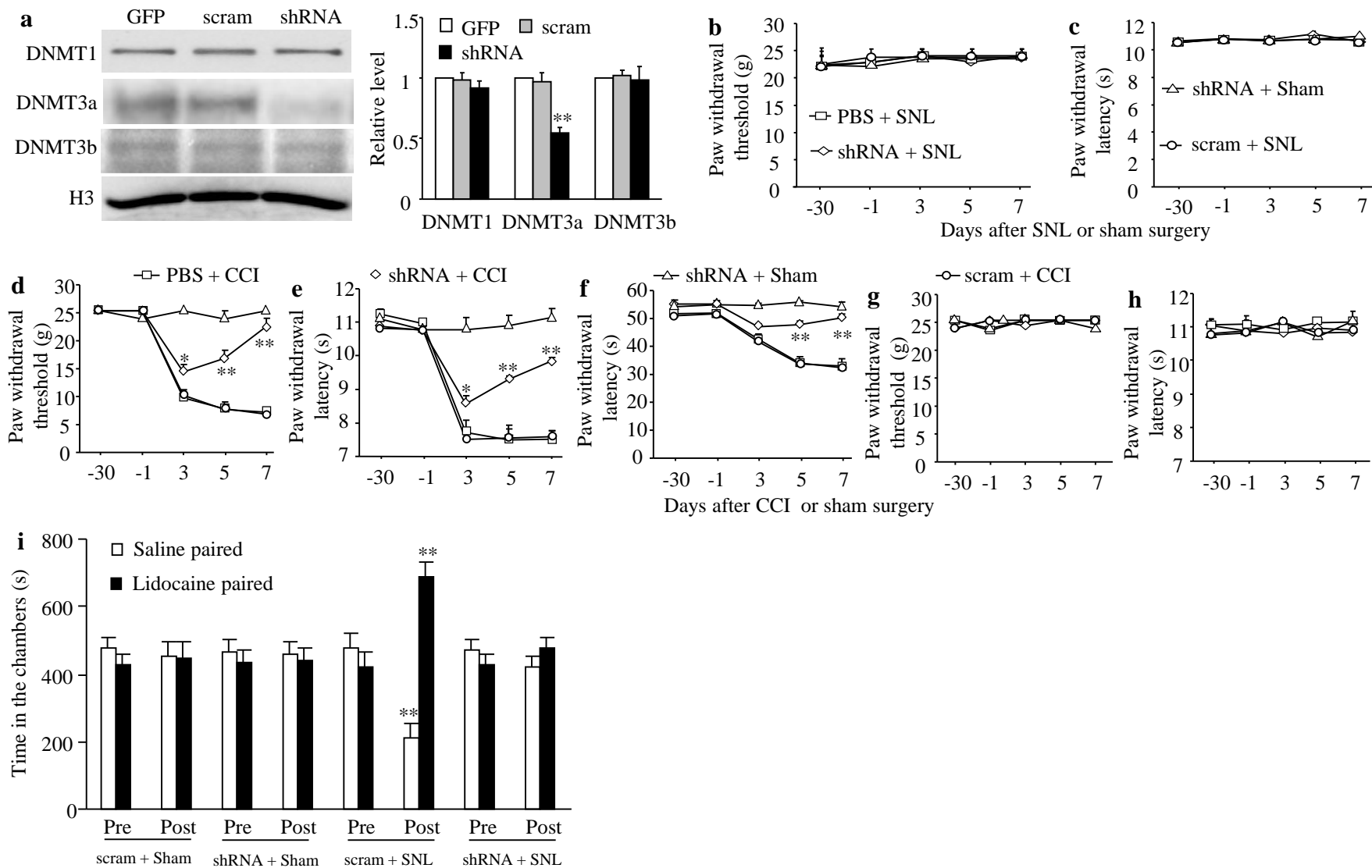
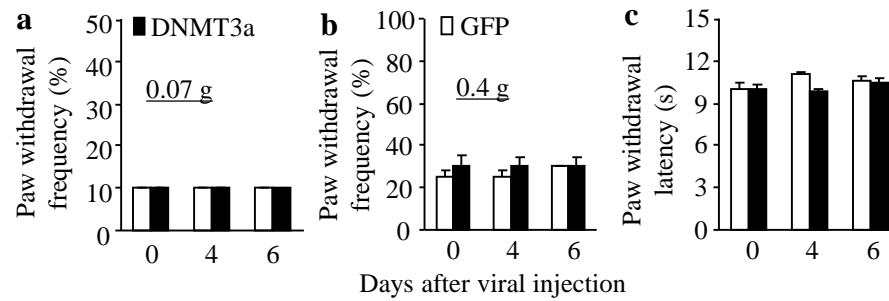


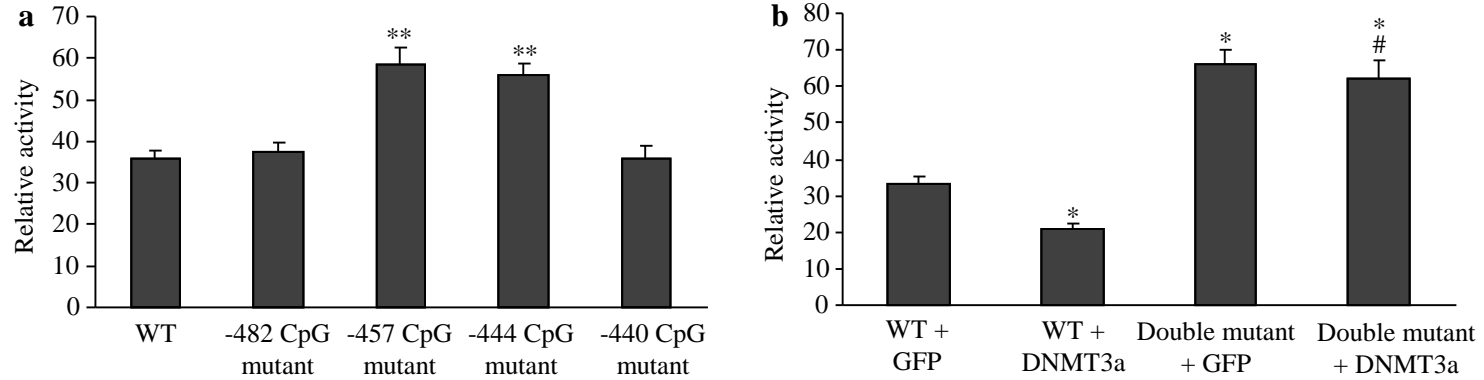
Supplementary Figure 1. (a) Levels of DNMT3a and DNMT3b in the contralateral L5 DRG on days 0, 3, 7, and 14 post-SNL in rats. $n = 6$ rats/time point. One-way ANOVA (relative level vs. time points) followed by *post hoc* Tukey test, $F_{\text{time}}(3, 11) = 0.10$ for DNMT3a and $F_{\text{time}}(3, 11) = 0.27$ for DNMT3b. (b) Levels of DNMT3a and DNMT3b in the ipsilateral L4 DRG on days 0, 3, 7 and 14 post-SNL in rats. $n = 6$ rats/time point. One-way ANOVA (relative level vs. time points) followed by *post hoc* Tukey test, $F_{\text{time}}(3, 11) = 0.18$ for DNMT3a and $F_{\text{time}}(3, 11) = 0.17$ for DNMT3b. (c) Levels of DNMT3a and DNMT3b in the ipsilateral L5 dorsal horn on days 0, 3, 7 and 14 post-SNL in rats. $n = 6$ rats/time point. One-way ANOVA (relative level vs. time points) followed by *post hoc* Tukey test, $F_{\text{time}}(3, 15) = 0.87$ for DNMT3a and $F_{\text{time}}(3, 11) = 0.001$ for DNMT3b. (d) Levels of DNMT3a and DNMT3b in the ipsilateral L4 and L5 DRG at 0 h, 2 h, 1 d, 3 d, and 7 d post-CFA in rats. $n = 6$ rats/time point. One-way ANOVA (relative level vs. time points) followed by *post hoc* Tukey test, $F_{\text{time}}(4, 29) = 0.76$ for DNMT3a and $F_{\text{time}}(4, 14) = 1.49$ for DNMT3b. (e) Levels of TET1, TET2, and TET3 in the ipsilateral L5 DRG on days 0, 3, and 7 post-SNL in rats. $n = 12$ rats/time point. One-way ANOVA (relative level vs. time points) followed by *post hoc* Tukey test, $F_{\text{time}}(2, 8) = 0.70$ for TET1, $F_{\text{time}}(2, 8) = 0.76$ for TET2, and $F_{\text{time}}(2, 8) = 1.10$ for TET3. (f) Level of OCT1 in the contralateral (Con) L5 DRG and ipsilateral (Ipsi) L4 DRG on days 0, 3, and 7 post-SNL in rats. $n = 6$ rats/time point. One-way ANOVA (relative level vs. time points) followed by *post hoc* Tukey test, $F_{\text{time}}(2, 8) = 1.34$ for Con L5 DRG and $F_{\text{time}}(2, 8) = 0.66$ for Ipsi L4 DRG. Full-length blots are presented in Supplementary Figure 6.



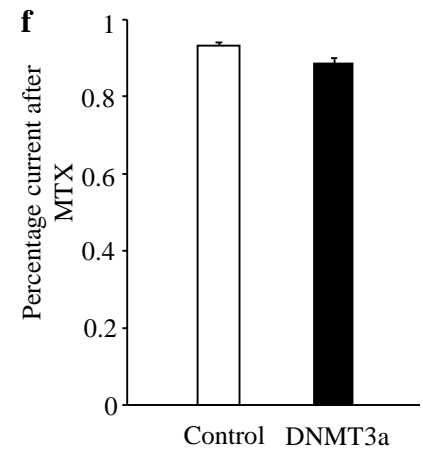
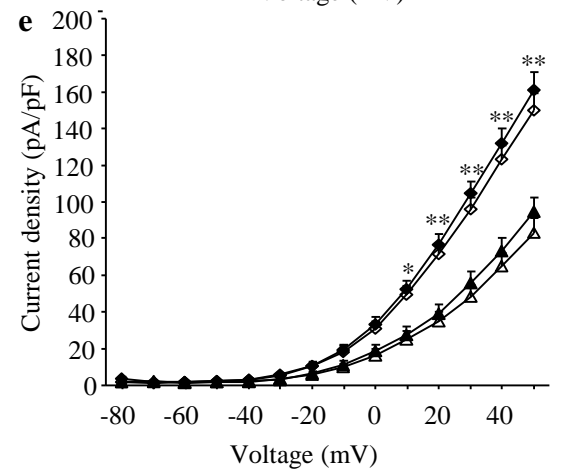
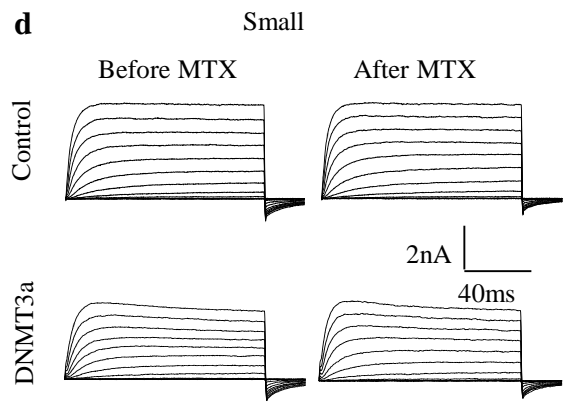
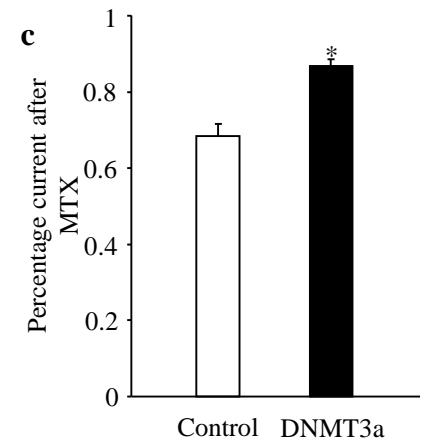
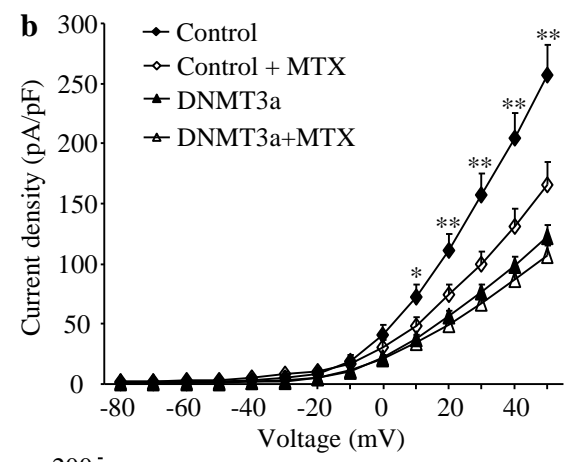
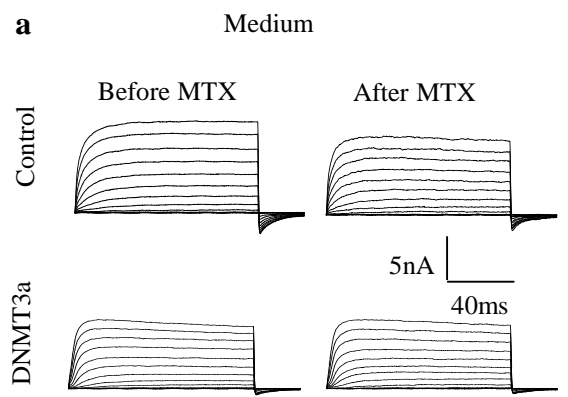
Supplementary Figure 2. (a) Levels of DNMT1, DNMT3a, and DNMT3b proteins in HEK-293T cells transfected with the vectors expressing *GFP* (control), scrambled *Dnmt3a* shRNA (scram), or *Dnmt3a* shRNA. $n = 3$ repeats/group. One-way ANOVA (relative level vs. group) followed by *post hoc* Tukey test, $F_{\text{group}}(2, 8) = 0.88$ for DNMT1, $F_{\text{group}}(2, 8) = 23.2$ for DNMT3a, and $F_{\text{group}}(2, 8) = 0.13$ for DNMT3b. $**P < 0.01$ vs the corresponding GFP-treated group. Full-length blots are presented in Supplementary Figure 6. (b, c) The effect of microinjection of AAV5-*Dnmt3a* shRNA (shRNA), AAV5-scrambled *Dnmt3a* shRNA (scram), or PBS into the ipsilateral L5 DRG on paw withdrawal responses to mechanical (b) and thermal (c) stimuli on the contralateral side at days shown before or after SNL or sham surgery in rats. $n = 5$ rats/group. Two-way ANOVA (effect vs. group \times time interaction) followed by *post hoc* Tukey test, $F_{\text{group}}(3, 124) = 0.13$ for (b) and $F_{\text{group}}(3, 124) = 0.63$ for (c). (d-h) The effect of microinjection of AAV5-*Dnmt3a* shRNA (shRNA), AAV5-scrambled *Dnmt3a* shRNA (scram), or PBS into the unilateral L4 and L5 DRG on paw withdrawal responses to mechanical (d, g), thermal (e, h) and cold (f) stimuli on the ipsilateral (d, e, f) and contralateral (g, h) sides at days shown before or after CCI or sham surgery in rats. $n = 5$ rats/group. Two-way ANOVA (effect vs. group \times time interaction) followed by *post hoc* Tukey test, $F_{\text{group}}(3, 129) = 126.3$ for (d), $F_{\text{group}}(3, 129) = 79.4$ for (e), $F_{\text{group}}(3, 119) = 73.6$ for (f), $F_{\text{group}}(3, 129) = 0.39$ for (g), and $F_{\text{group}}(3, 129) = 1.33$ for (h). $*P < 0.05$ or $**P < 0.01$ vs the corresponding PBS plus CCI group. (i) The effect of microinjection of AAV5-*Dnmt3a* shRNA (shRNA) or AAV5-scrambled *Dnmt3a* shRNA (scram) into the ipsilateral L5 DRG on the duration of time spent in saline- or lidocaine-paired chambers on day 7 post-SNL or sham surgery in rats. Pre: preconditioning. Post: post-conditioning. $n = 5$ rats/group. $**P < 0.01$ vs the corresponding preconditioning by two-tailed paired Student's *t* test.



Supplementary Figure 3. Paw withdrawal responses to mechanical (a, b) and thermal (c) stimuli on the contralateral side at days as shown from control HSV-*GFP* (GFP)- or HSV-*Dnmt3a* (DNMT3a)-injected mice. $n = 10/\text{group}$. Two-way ANOVA (effect vs. group \times time point interaction) followed by *post hoc* Tukey test, $F_{\text{group}}(1, 23) = 0.00$ for (a), $F_{\text{group}}(1, 23) = 1.2$ for (b), and $F_{\text{group}}(1, 23) = 3$ for (c).



Supplementary Figure 4. (a) *Kcna2* gene promoter activity in HEK-293 cells transfected with wild type (WT) vector expressing the fragment (-622 to +74) of *Kcna2* gene or with the vectors expressing this fragment with a mutated base at the -482, -457, -444, or -440 CpG site. n = 3 repeats/treatment. One-way ANOVA (relative activity vs. group) followed by *post hoc* Tukey test, $F_{\text{group}}(4, 14) = 137.9$. ** $P < 0.01$ vs the WT group. (b) *Kcna2* gene promoter activity in HEK-293 cells co-transfected with WT vector plus vector expressed GFP (GFP), WT vector plus vector expressing full-length *Dnmt3a* (DNMT3a), the vector expressing two mutated bases at the -457 and -444 CpG sites (double mutant) plus GFP, or the double mutant plus DNMT3a. n = 3 repeats/treatment. One-way ANOVA (relative activity vs. group) followed by *post hoc* Tukey test, $F_{\text{group}}(3, 11) = 391.8$. * $P < 0.05$ vs the WT plus GFP group. # $P < 0.05$ vs the WT plus DNMT3a group.



Supplementary Figure 5. *Dnmt3a* overexpression reduces total Kv current density in medium and small neurons from the injected DRG 6–8 weeks after viral microinjection into the unilateral L4 and L5 DRG in rats. (a) Representative traces of total Kv current in medium DRG neurons from AAV5-*GFP* (Control)-treated and AAV5-*Dnmt3a* (DNMT3a)-treated groups before or after bath perfusion of 100 nM maurotoxin (MTX). (b) I-V curve for control (n = 22 neurons, 6 rats) and DNMT3a-treated (n = 27 neurons, 8 rats) medium DRG neurons before or after 100 nM MTX treatment. The current density was plotted against each voltage. One-way ANOVA (current density vs. group) followed by *post hoc* Tukey test, $F_{\text{group}}(1, 13) = 50.8$. $*P < 0.05$, $**P < 0.01$ vs the corresponding DNMT3a-treated group at the same voltage. (c) At +50 mV, the reduction in total Kv current after MTX treatment in medium DRG neurons was greater in the control group than in the DNMT3a-treated group. $**P < 0.01$ vs control group by two-tailed unpaired Student's *t*-test. (d) Representative traces of total Kv current in small DRG neurons from control and DNMT3a-treated groups before or after bath perfusion of 100 nM MTX. (e) I-V curve for control (n = 23 neurons, 8 rats) and DNMT3a-treated (n = 24 neurons, 9 rats) small DRG neurons before or after 100 nM MTX treatment. The current density was plotted against each voltage. One-way ANOVA (current density vs. group) followed by *post hoc* Tukey test, $F_{\text{group}}(1, 13) = 68.7$. $*P < 0.05$, $**P < 0.01$ vs the corresponding DNMT3a-treated group at the same voltage. (f) At +50 mV, the reduction in total Kv current after MTX treatment in small DRG neurons was similar between the control group and the DNMT3a-treated group.

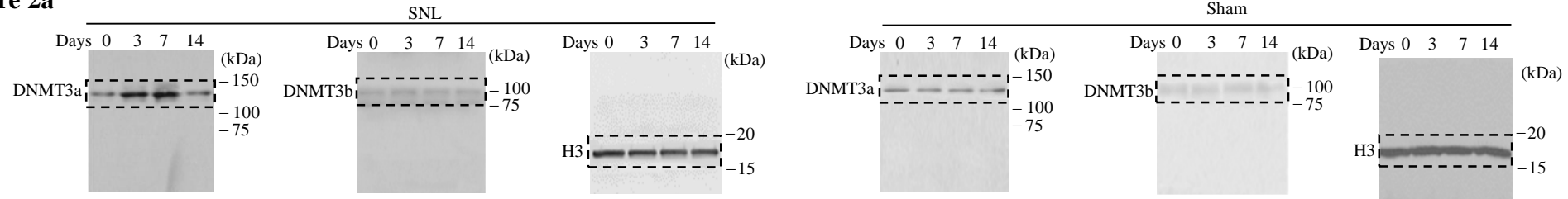
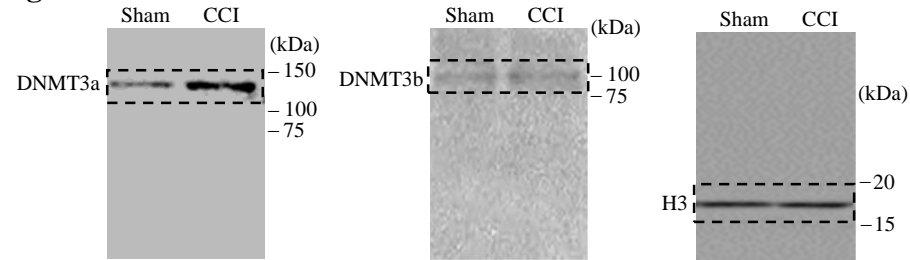
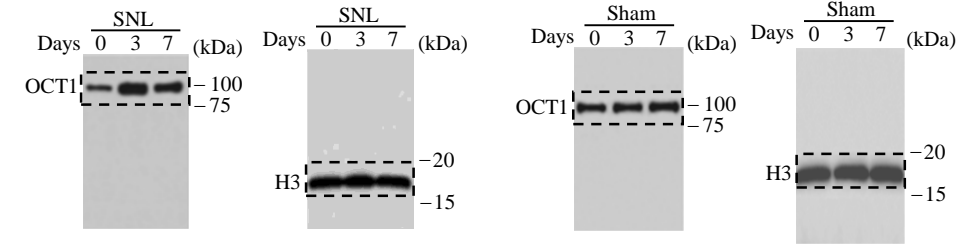
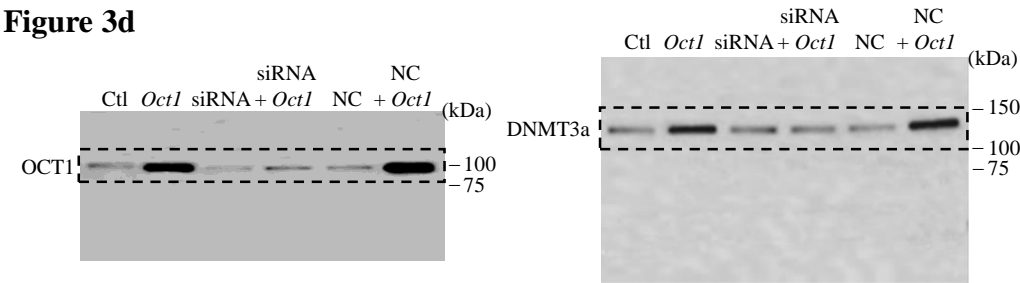
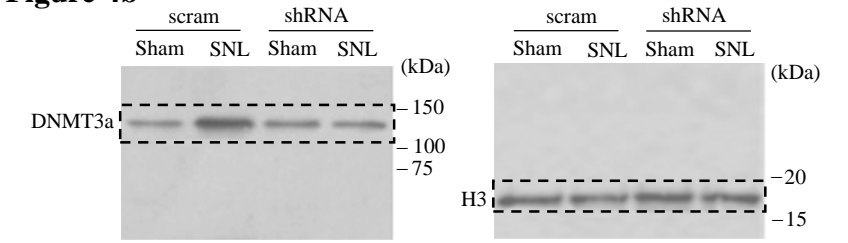
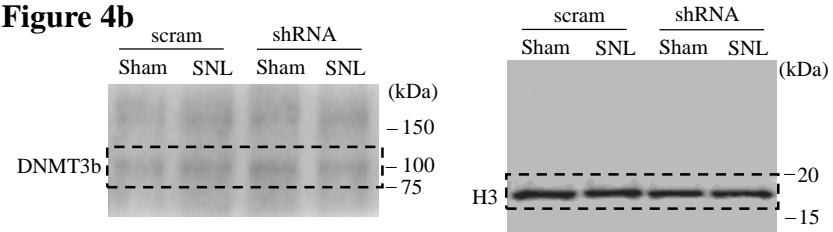
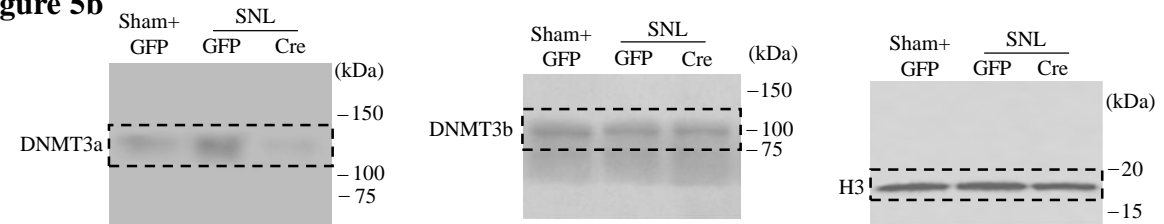
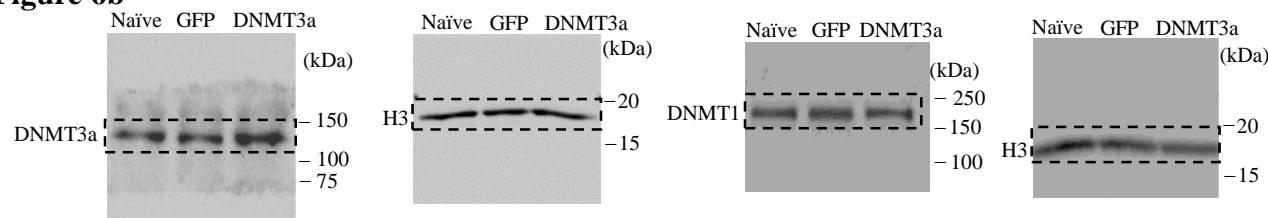
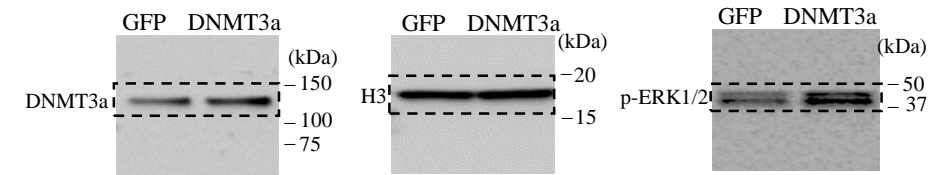
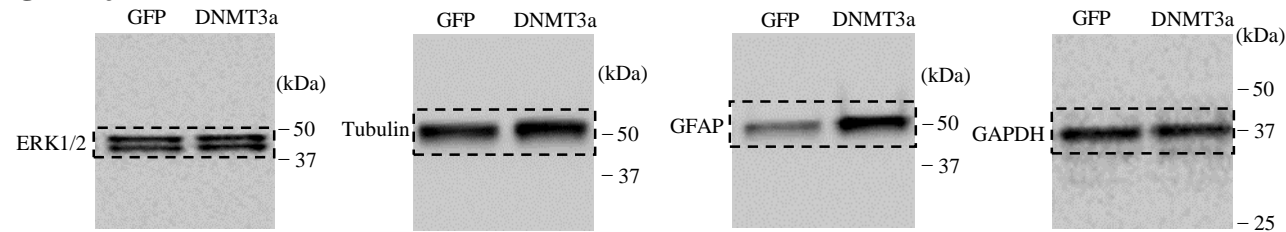
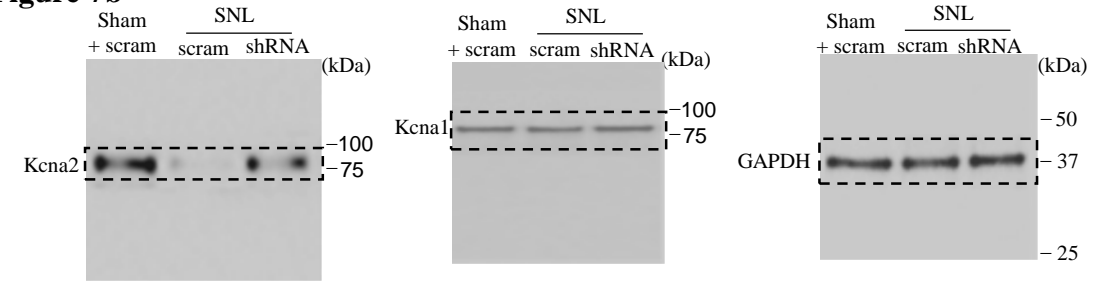
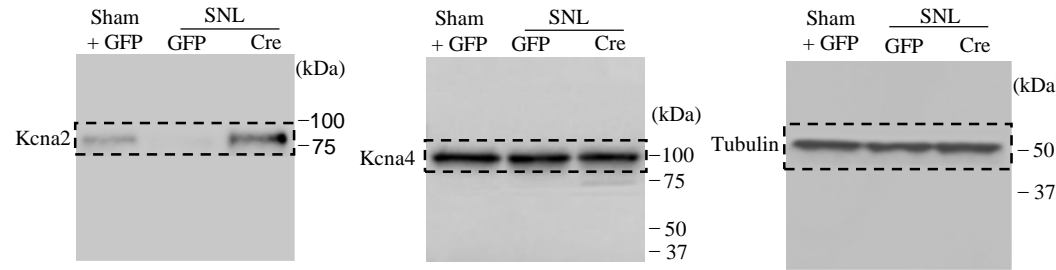
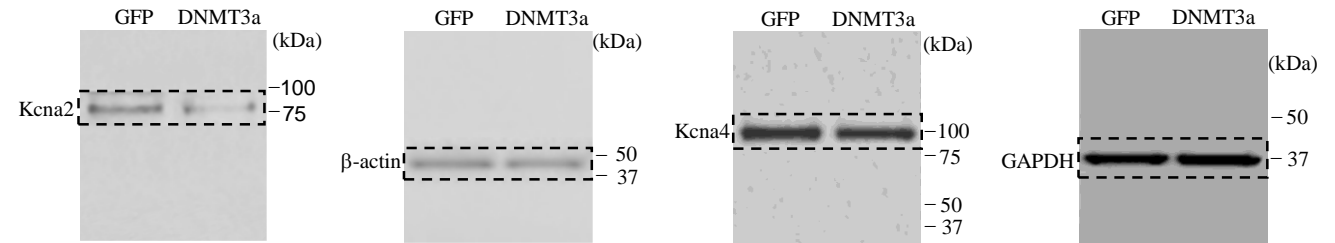
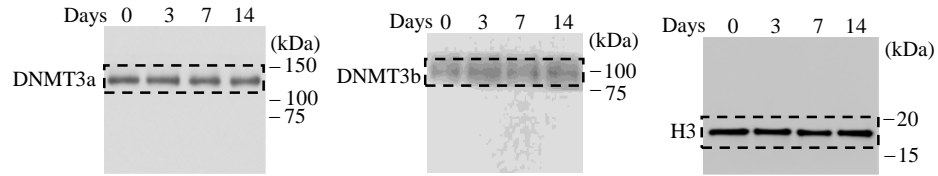
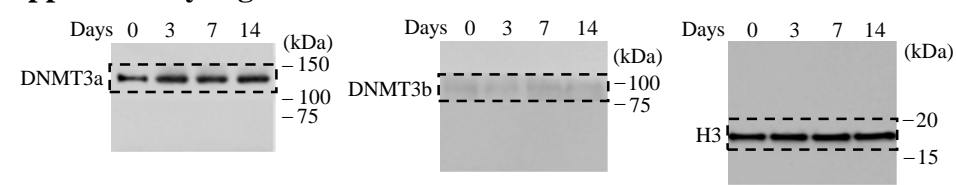
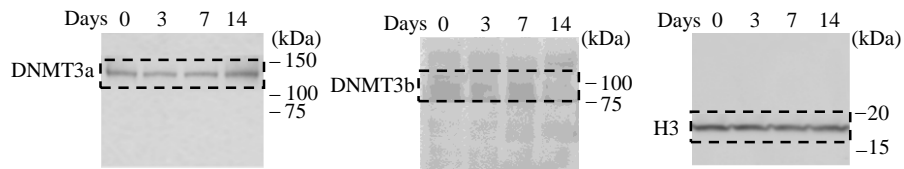
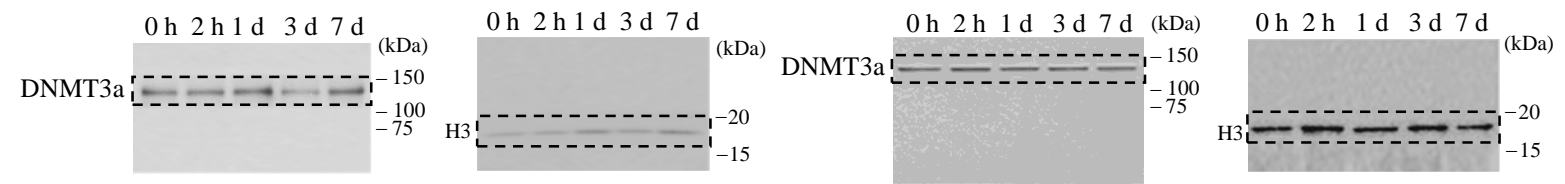
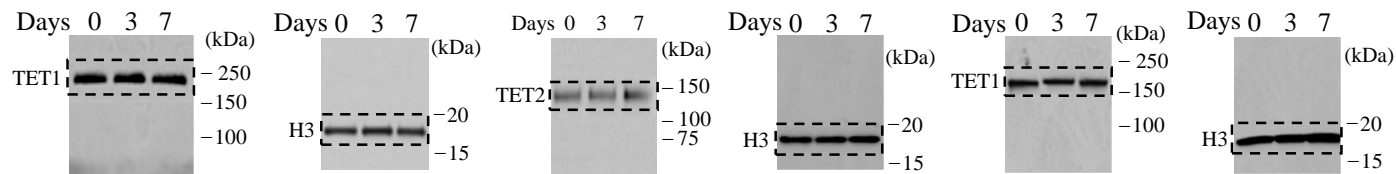
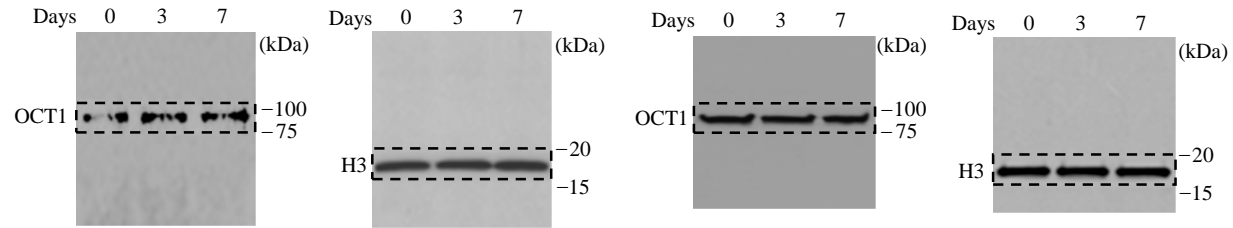
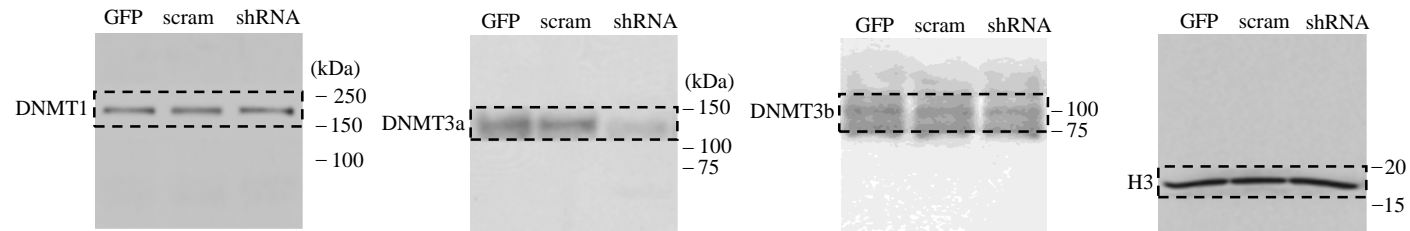
Figure 2a**Figure 2e****Figure 3b****Figure 3d****Figure 4b****Figure 4b****Figure 5b****Figure 6b****Figure 6j**

Figure 6j**Figure 7b****Figure 7d****Figure 8b****Supplementary Figure 1a****Supplementary Figure 1b****Supplementary Figure 1c****Supplementary Figure 1d****Supplementary Figure 1e**

Supplementary Figure 1f



Supplementary Figure 2a



Supplementary Figure 6. Full-length pictures of the blots presented in the main figures and supplemental figures.

Supplementary Table 1. Locomotor test after viral injection

Treated groups	Placing	Grasping	Righting
PBS + SNL (rats)	5 (0)	5 (0)	5 (0)
AAV5-shRNA + SNL	5 (0)	5 (0)	5 (0)
AAV5-scram + SNL	5 (0)	5 (0)	5 (0)
AAV5-shRNA + Sham	5 (0)	5 (0)	5 (0)
AAV5-scram + Sham	5 (0)	5 (0)	5 (0)
PBS + CCI (rats)	5 (0)	5 (0)	5 (0)
AAV5-scram + CCI	5 (0)	5 (0)	5 (0)
AAV5-shRNA + CCI	5 (0)	5 (0)	5 (0)
PBS + SNL (mice)	5 (0)	5 (0)	5 (0)
AAV5-GFP + Sham	5 (0)	5 (0)	5 (0)
AAV5-GFP + SNL	5 (0)	5 (0)	5 (0)
AAV5-Cre + SNL	5 (0)	5 (0)	5 (0)
AAV5-Cre + Sham	5 (0)	5 (0)	5 (0)
AAV5- <i>Dnmt3a</i>	5 (0)	5 (0)	5 (0)
AAV5-GFP	5 (0)	5 (0)	5 (0)
HSV- <i>Dnmt3a</i>	5 (0)	5 (0)	5 (0)
HSV-GFP	5 (0)	5 (0)	5 (0)

N = 5-8/group; 5 trials; Mean (SEM)

Supplementary Table 2: Membrane input resistance and other action potential parameters in DRG neurons.

	Large Cell			Medium Cell			Small Cell		
	GFP	DNMT3a	t/p value	GFP	DNMT3a	t/p value	GFP	DNMT3a	t/p value
n	25cells, 5 rats	22cells, 5rats		25cells, 5rats	24cells, 5rats		13cells, 5rats	15cells, 5rats	
R _{in} , MΩ	45.40±2.62	50.45±3.36	-1.200/0.236	40.76±2.61	43.43±3.32	-0.634/0.529	47.17±4.51	53.99±8.11	-0.734/0.469
APT, mV	-13.68±0.96	-11.16±0.81	1.973/0.055	-14.40±0.94	-14.43±1.18	0.019/0.985	-16.43±1.71	-16.66±2.16	0.082/0.936
APO, mV	46.10±3.79	50.28±3.12	-0.838/0.407	48.17±3.02	48.52±3.15	-0.079/0.938	39.13±2.19	34.90±3.93	0.940/0.355
APA, mV	100.35±3.42	97.53±2.93	0.618/0.540	103.66±3.34	97.52±3.52	1.268/0.211	86.65±4.04	82.14±5.00	0.700/0.490
AHPA, mV	-19.19±1.14	-20.40±1.52	-0.650/0.519	-18.79±1.25	-18.49±1.31	-0.165/0.869	-14.86±0.86	-17.52±1.12	1.530/0.139

Values are Mean ± S.E.M., R_{in}: membrane input resistance. APT: action potential threshold. APA: action potential amplitude. APO: action potential overshoot. AHPA: afterhyperpolarization amplitude. All values are mean ± S.E.M. student t-test.

Supplementary Table 3 All primers used

Names	Sequences (5'-3')	Names	Sequences (5'-3')	Names	Sequences (5'-3')
PCR/Real-time PCR		ChIP-PCR		rKCNA2-N-F3	GGTTAGGGTATTTATTTGTAAGGGTAA
RT-rat KCNA2	GGGTGACTCTCATCTTTGGA	rKCNA2-ChIP-F1	GGGGCAAAGACAACAGTGAAT	rKCNA2-N-R3	CTATACAATCAACTACACTTCCCATCA
RT-mouse KCNA2	GTCCCCGTCACATCTTCTCAC	rKCNA2-ChIP-R1	CCAACATAATGAAGTAGGCAGG	rKCNA2-F4	TTTGTGGTTTGTGYGTGATATA
Rat-KCNA2-F	CCCATCTGCAAGGGCAACGT	rKCNA2-ChIP-F2	CTGTCTGGCAGCATCGTAATAA	rKCNA2-R4	CCTAAACTCTAAAAATACAAAACAAT
Rat-KCNA2-R	CACAGCCTCCTTTGGCTGGC	rKCNA2-ChIP-R2	CACTGCCACCACTGAGCTGT	rKCNA2-N-F4	GTGATGGGAAGTGTAGTTGAT
Rat-DNMT3A-F	GTGGTTCGGAGATGGCAAAT	rKCNA2-ChIP-F3	GGGGATCTAACCCAATGGAC	rKCNA2-N-R4	ACCCAAATCTAACTTCCTCTTC
Rat-DNMT3A-R	TGGAGGACTTCGTAGATGGCT	rKCNA2-ChIP-R3	TGGGTGATAGACAGGGCAGG	Cloning	
Rat-DNMT3B-F	CGCAGGACGTGGTAGGAGATG	rKCNA2-ChIP-F4	CTGCCTGCCCTGTCTATCAC	rOCT1-F	AAATGGCGGACGGAGGAG
Rat-DNMT3B-R	ACTGTTGCTGTTTCGGGGTTC	rKCNA2-ChIP-R4	CCCATTCCATGCACTCTTCT	rOCT1-R	ACAGGCGTCATGTTTTAGCC
Rat-DNMT1-F	CGAGTGCCTGCACTTGCC	rKCNA2-ChIP-F5	ACCCCTGATGTCGGCCTAGA	rOCT1-N-F	ATATCTAGAGCCACCATGGCGGACGGAGG
Rat-DNMT1-R	TCCTCTTTATGTAGTTTGGTTTCC	rKCNA2-ChIP-R5	GCAGAGAAGCCCATTTACT	rOCT1-N-R	CGATAGGATCCTCACTGTGCCTTGGAGGC
Rat-OCT1-F	CACTTCCACAGAGCCAGACA	rDNMT3A-ChIP-F	ACCCAAAGAGTGCAGCAAAC	rDNMT3A-Luci-F	TATAGGTACCAGGAACCGTTGTGTGTCTCC
Rat-OCT1-R	GGTGGTTTGGCTGAAATCAT	rDNMT3A-ChIP-R	GTGGAGGAGGAAGTGAGCAG	rDNMT3A-Luci-R	TCGCAAGCTTTCGTGGTCTTTGTGAGCAAG
Rat-GAPDH-F	TCGGTGTGAACGGATTTGGC	Bisulfite Sequencing		rDNMT3AshRNA-F	TTACCGGTGGGCAGGAAGAGGGCCTATTTC CCATGA
Rat-GAPDH-R	CCTTCAGGTGAGCCCCAGC	rKCNA2-F1	GTAGAAATAGAAGATTGGAGTGG	rDNMT3A-shRNA-R	AA <u>TCTAG</u> ACATCCACTGTGAATGATAACGA ATTCACTTATCATTACAGTGGATGGGATCC TCGTCCTTTCCACAAGATAT
Mouse-KCNA2-F	CTGCAAGGGCAACGTCACAC	rKCNA2-R1	CTAAAACCAAAACTAACRAAATA	rKCNA2-Luci-F	CGA <u>CGCGT</u> CGCCTTCACCTGCTGTATTGCC TGGGAA
Mouse-KCNA2-R	GGGACAGTGAGATGCTTGGC	rKCNA2-N-F1	GGTTTGTAGATTTTGTGGTAGT	rKCNA2-Luci-R	GAAGATCTTCTTGCAGATGGGTACCCGAGC CTCCAT
Mouse-DNMT3A-F	GCCAAGAAACCCAGAAAGAGC	rKCNA2-N-R1	CACTACCACCACTAAACTATCCAT		
Mouse-DNMT3A-R	GCACATGCCTCCAATGAAGA	rKCNA2-F2	TAGGGTTTTATTAAGAATGGGGT		
Mouse-DNMT3B-F	CAGCCTTCTGAATTACACGCA	rKCNA2-R2	ACACTAATTTACCCTTACAAAT		
Mouse-DNMT3B-R	TCCCATTGCTATGTCGGGTT	rKCNA2-N-F2	ATAAGGGGATTTAATTTAATGGAT		
Mouse-DNMT1-F	AGTCGGACAGTGACACCCTTT	rKCNA2-N-R2	TACCCCAACCTCCATATTCCTAAA		
Mouse-DNMT1-R	TGTGTCTACAACCTCTGCGTTTCT	rKCNA2-F3	GTTTATTATTTAGGAATATGGAGG		
Mouse-GAPDH-F	TCGGTGTGAACGGATTTGGC	rKCNA2-R3	AATCCTACCCACCCACTAT		
Mouse-GAPDH-R	TCCCATTCTCGGCCTTGACT				

RT: Reverse-transcription. F: Forward. R: Reverse. N-PCR: Nested PCR. Underlined letters: the restriction enzyme recognition sites.