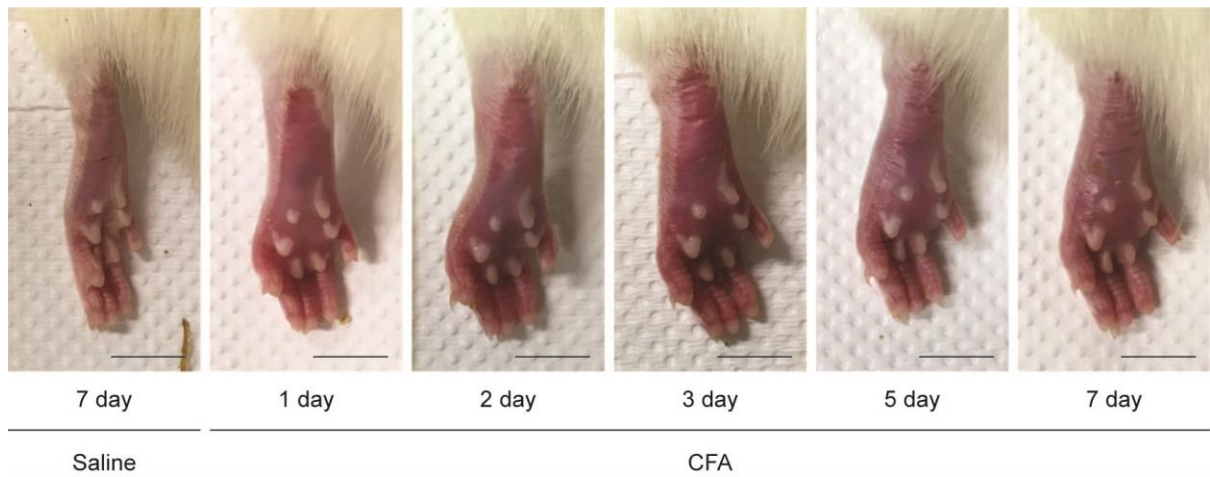


Supplementary materials

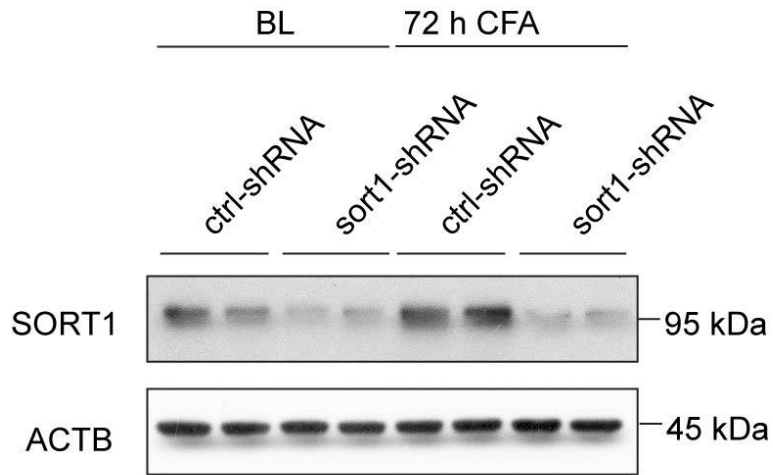
Supplementary Figure S1. Classical signs of the left hind paw of rat CFA chronic inflammatory pain model.

Photograph of left hind paw of the rat receiving vehicle (saline) or CFA intraplantar injection for a total time course of 7 days. Scale bar represents 1 cm.



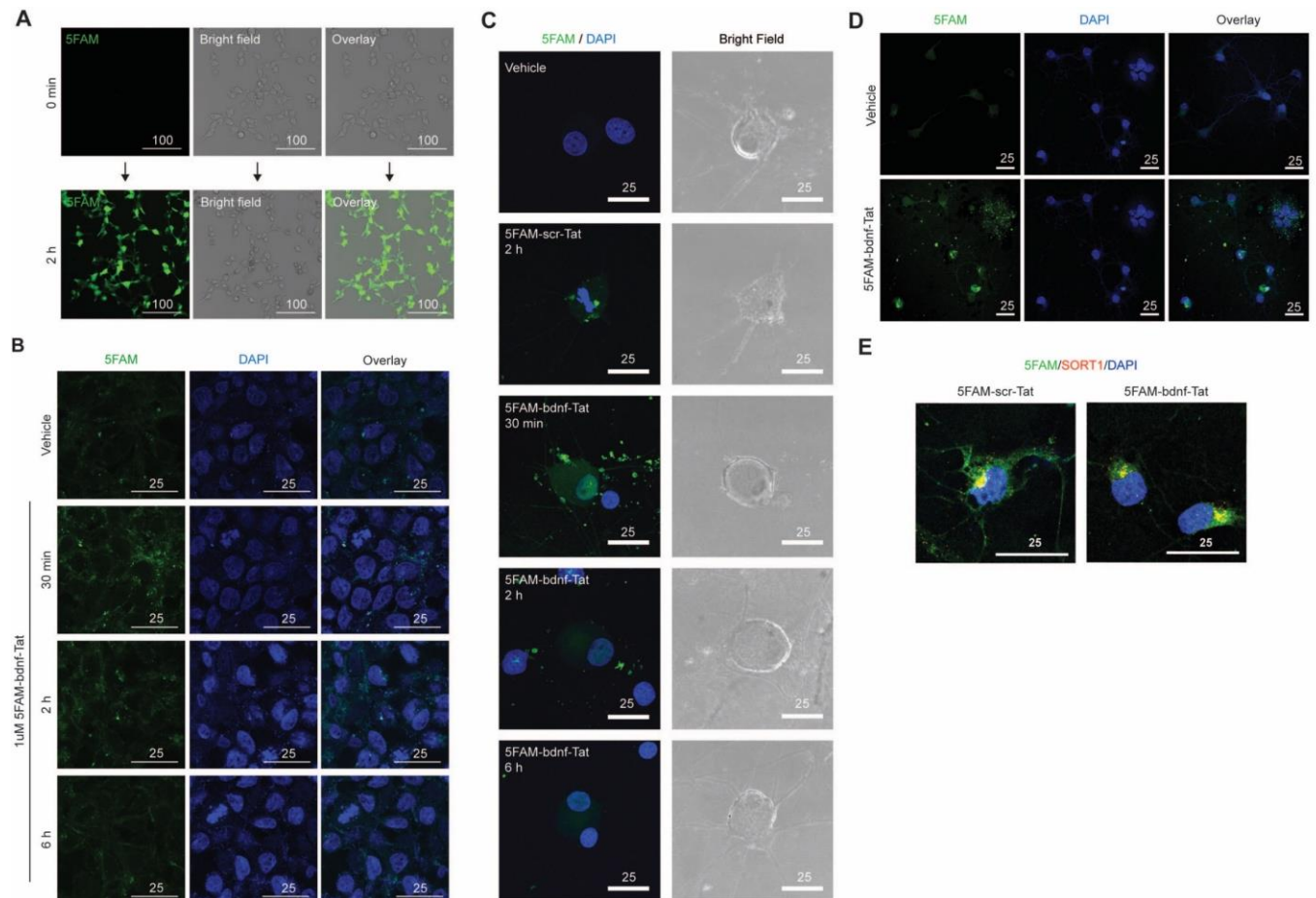
Supplementary Figure S2. *In Vivo* sortilin knockdown efficiency

Immunoblots of L5 DRG tissues after DRG injection with control-shRNA (ctrl-shRNA) or sortilin-targeted shRNA (sort1-shRNA) obtained with antibodies against sortilin or β -actin. Samples were collected before (baseline) and 3 days after CFA injection. Each lane represents sample obtained from a single rat. BL, Baseline.



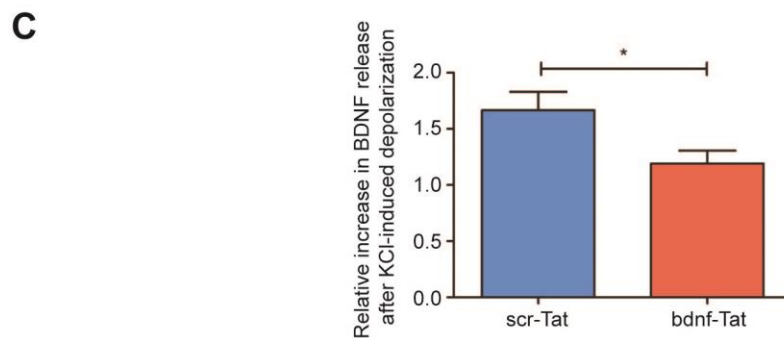
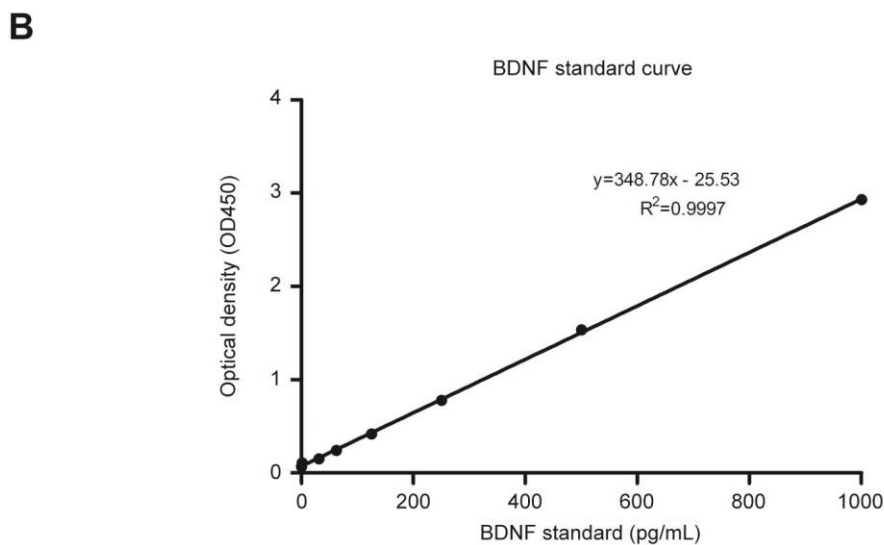
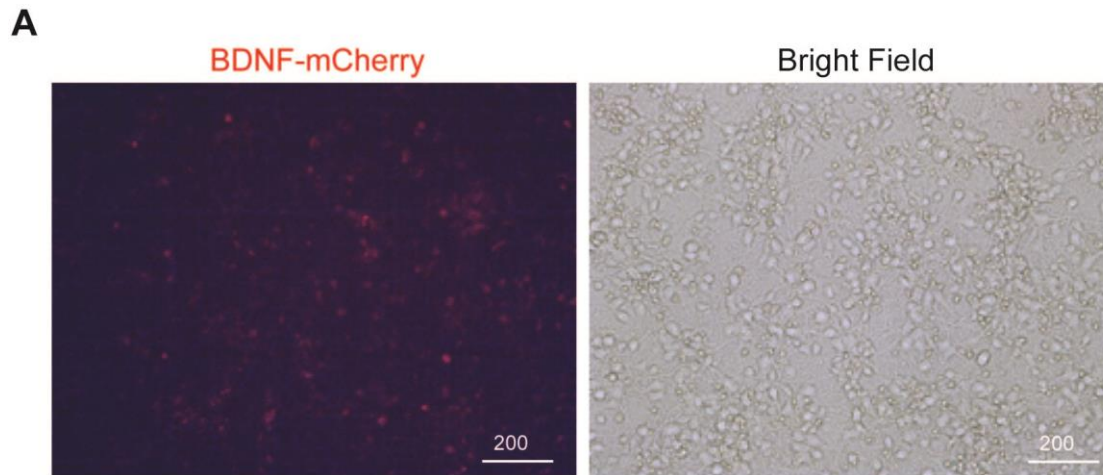
Supplementary Figure S3. Delivery of Tat-tagged peptides into HEK293 cells, DRG and cortical neuronal cultures and its colocalization with endogenous sortilin.

(A) Live fluorescence micrograph of 5FAM (green) or bright field in HEK293 cell cultures obtained just before and 2 h after 5 μ M 5FAM-bdnf-Tat incubation. Scale bars represent 100 μ m. (B) Fluorescence micrograph of 5FAM (green) or DAPI (blue) in fixed HEK293 cell cultures incubated with vehicle or 1 μ M 5FAM-bdnf-Tat for 30 min, 2 h or 6 h. Scale bars represent 25 μ m. (C) Fluorescence micrograph of 5FAM (green), DAPI (blue) or bright field in fixed rat DRG neuronal cultures incubated with 1 μ M 5FAM-tagged scr89-98-Tat (scr-Tat) or 5FAM-tagged bdnf89-98-Tat (bdnf-Tat) for 30 min, 2 h and 6 h. Scale bars represent 25 μ m. (D) Fluorescence micrograph of 5FAM (green) or DAPI (blue) in fixed rat primary cortical neuronal cultures incubated with vehicle or 1 μ M 5FAM-bdnf-Tat for 2 h. Scale bars represent 25 μ m. (E) Fluorescence micrograph of 5FAM (green), sortilin (red) or DAPI (blue) in rat primary hippocampal neuronal cultures incubated with 1 μ M 5FAM-scr-Tat (*Left*) or 5FAM-bdnf-Tat (*Right*) for 30 min. Scale bars represent 25 μ m.



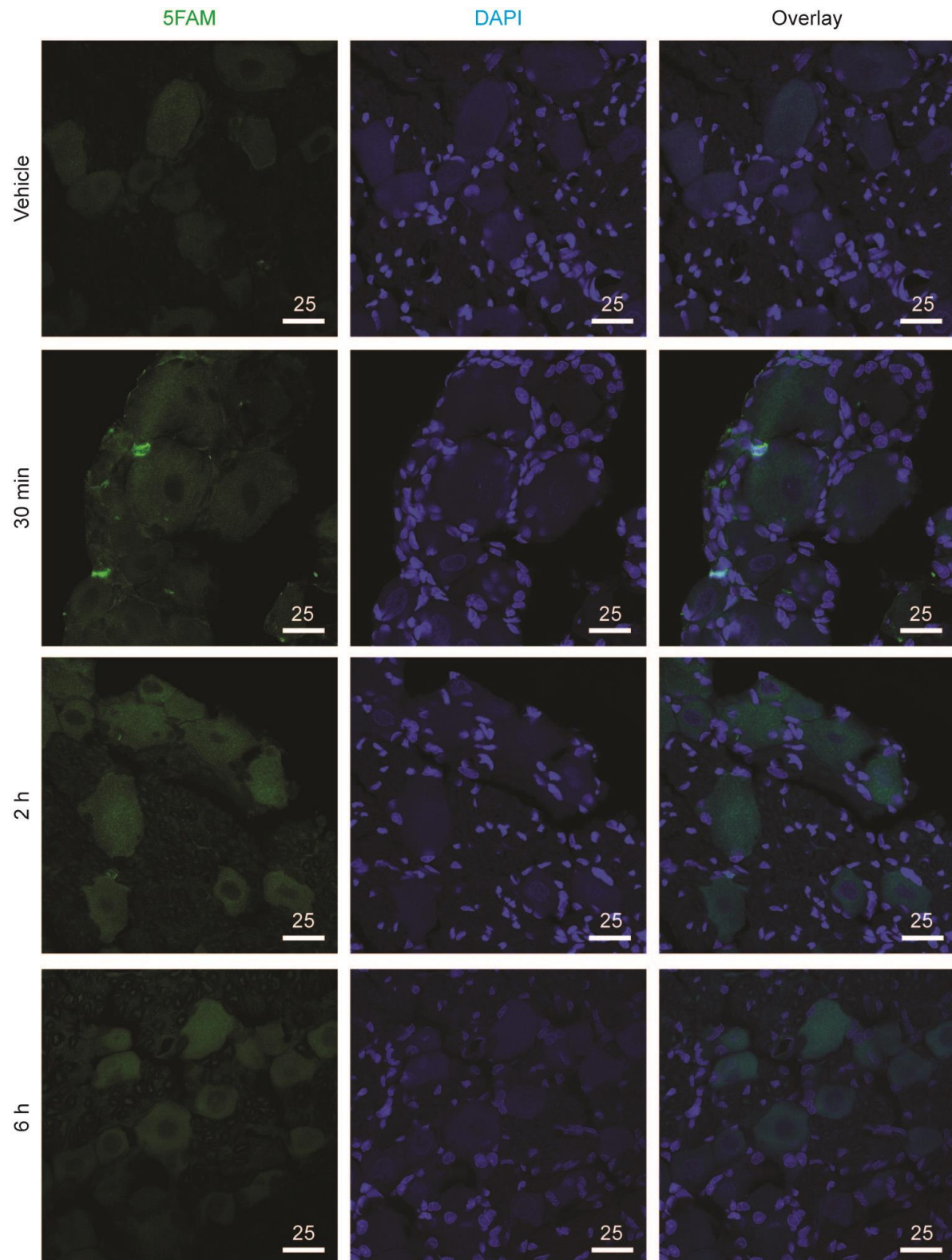
Supplementary Figure S4. ELISA of primary rat cortical neuronal culture overexpressing BDNF.

(A) Overexpression of BDNF-mCherry (red) into rat primary cortical neuronal culture was mediated by lentiviral transduction for 72 h. Scale bars represent 200 μm . (B) Standard Curve of BDNF ELISA for protein quantification. Recombinant human BDNF was used as standards. (C) Effect of 30 min peptide pre-treatment on activity-dependent secretion of BDNF in rat cortical neuronal cultures with high-potassium stimulus using ELISA. $*P < 0.05$, Student's *t*-test. Values are means \pm SEM. $n = 9$ samples obtained from 3 independent experiments.



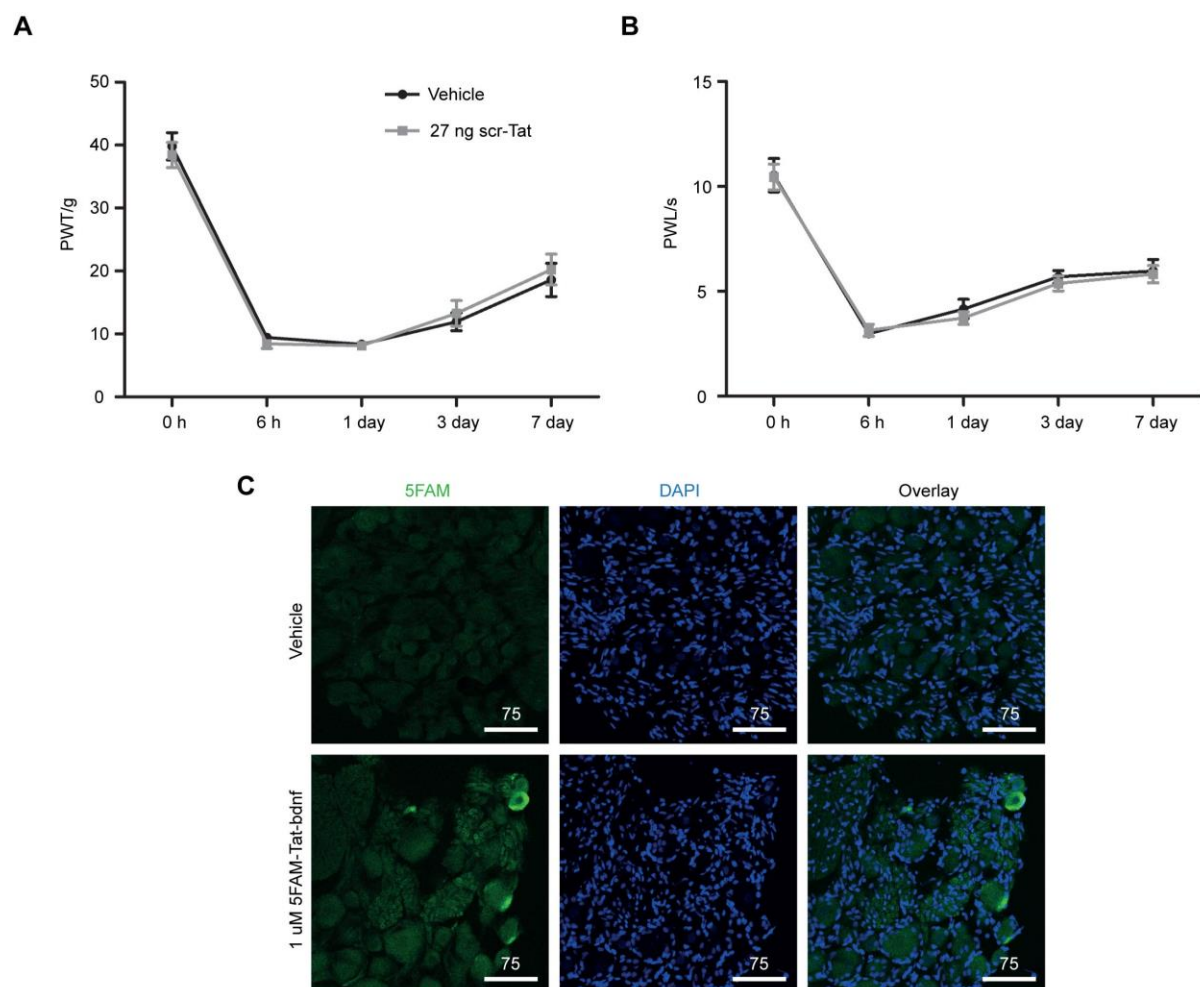
Supplementary Figure S5. Penetration of the intrathecally introduced blocking peptide into rat DRGs.

Fluorescence micrograph of 5FAM (green) or DAPI (blue) in rat L4-L5 DRG tissues of rat receiving 5FAM-bdnf-Tat intrathecal injection. Scale bars represent 25 μm .



Supplementary Figure S6. Effects on behavioural changes in rats with intrathecal injection scr-Tat and penetration of the intravenously introduced peptide into rat DRGs.

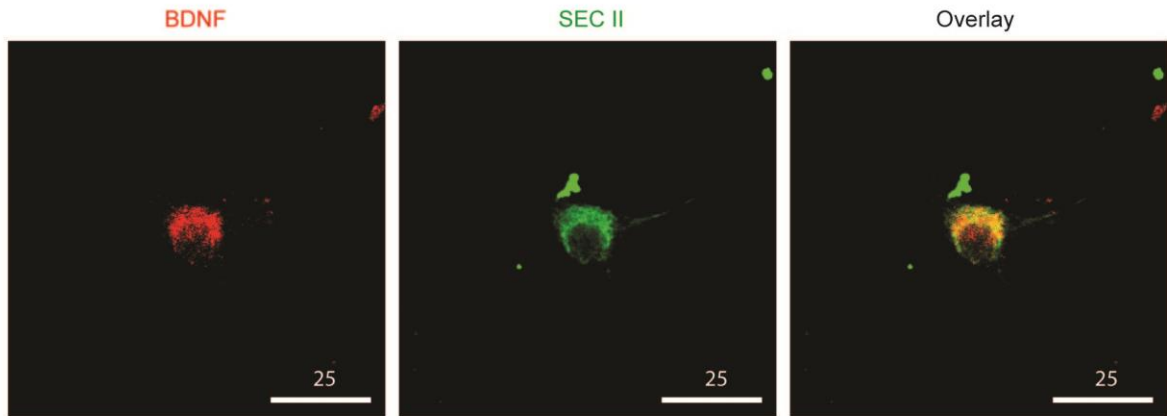
(A) Effect of intrathecal injection of vehicle or 27 ng scr-Tat on mechanical allodynia of the rat CFA model. Results are presented as pain withdrawal threshold (PWT) in grams. $P = 0.948$, two-way ANOVA with repeated measures. Values are means \pm SEM. $n = 8$. (B) Effect of intrathecal injection of vehicle or 27 ng scr-Tat on thermal hyperalgesia of the rat CFA model. Results are presented as pain withdrawal latency (PWL) in seconds. $P = 0.566$, two-way ANOVA with repeated measures. Values are means \pm SEM. $n = 8$. (C) Fluorescence micrograph of 5FAM (green) or DAPI (blue) in rat L4-L5 DRG tissues of rat receiving 5FAM-bdnf-Tat intravenous injection. Scale bars represent 75 μ m.



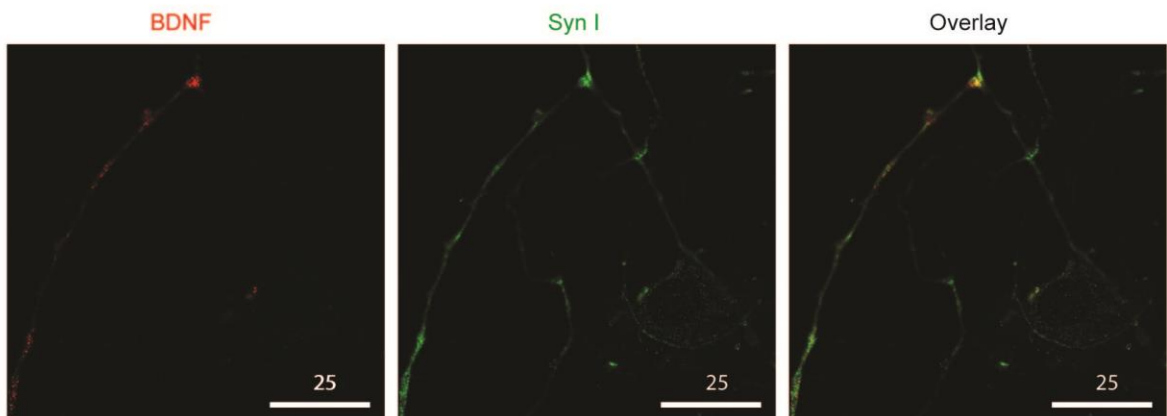
Supplementary Figure S7. The regulated secretion of BDNF from DRG into the first synaptic process.

(A) Fluorescence micrograph of BDNF(red) or SECII (green) in rat DRG neuronal. Scale bars represent 25 μm . (B) Fluorescence micrograph of BDNF(red) or SynI (green) in rat DRG neuronal. Scale bars represent 25 μm .

A



B



Supplementary Figure S8. BLAST results of human BDNF and human NGF protein sequence.

Reference protein sequences of human BDNF (GenBank: CAA62632.1) and NGF (GenBank: CAA37703.1) obtained from National Center for Biotechnology Information (NCBI) were subjected to BLAST program (NCBI, Bethesda, MD) for protein alignment. The sequence used for the blocking peptide design was highlighted in yellow. Query ID: CAA62632.1 (BDNF); Subject ID: CAA37703.1 (NGF).

CAA37703.1 nerve growth factor [Homo sapiens]
 Sequence ID: Query_131685 Length: 257 Number of Matches: 1

Range 1: 60 to 256 [Graphics](#) ▼ Next Match ▲ Previous Match

Score	Expect	Method	Identities	Positives	Gaps
169 bits(429)	7e-57	Compositional matrix adjust.	94/212(44%)	125/212(58%)	19/212(8%)
BDNF Query 40	HGTLESVNGPKAGSRGLTSLADTFEHVIE---ELLDEDHKVRPNEENNKDADLYTSRVML				96
	TL P+ RG + F+ VI ELL + + + RV+L				
NGF Sbjct 60	QSTLPKAEAPREPERGGPA-KSAFQPVIAMDTELLRQRRYN-----SPRVLL				106
BDNF Query 97	SSQVPLEPPLLFLLEEKNYLDAANMSMMVLRHSD-PARRGELSVCDSEWVTAADKKT				155
	S PLEPP L+L+E+Y AN + R+++ + RGE SVCDS S WVT DK +				
NGF Sbjct 107	SDSTPLEPPPLYLMEDYVGGSPVVANRTSRRKRYAEHKSHRGEYSVCDSSESLWVT--DKSS				164
BDNF Query 156	AVDMSGGTVTVLEKVPVSKGQLKQYFYETKCNPMGYTKEGCRGIDKRHWNSQCRTTQSYV				215
	A+D+ G VTVL ++ +KQYFYET+C K GCRGID +HWNSQC+T+Q+YV				
NGF Sbjct 165	AIDIRGHQVTVLGEIKTGNSPVKQYFYETRCKEARPVKNGCRGIDDKHWNSQCCKTSQTYV				224
BDNF Query 216	RALTMSKKRIGWRFIRIDTSCVCTLTIKRGR 247				
	RALT ++ K +GWR+IRIDTSCVC L+ K GR				
NGF Sbjct 225	RALTSENNKLVGWRWIRIDTSCVCALSRKIGR 256				