Chemokine receptor 2 (CCR2) mediates mechanical and cold hypersensitivity in chronic sickle cell disease pain

Kate Sadler, PhD

Medical College of Wisconsin

Acknowledgements

Stucky Lab
Cheryl Stucky, PhD
Kate Sadler, PhD
Francie Moehring
Ashley Reynolds
Crystal O'Hara
Tony Menzel
Sarah Langer
Kate Zappia, PhD
Andy Weyer, PhD

University of Pittsburgh
Cheryl Hillery, MD

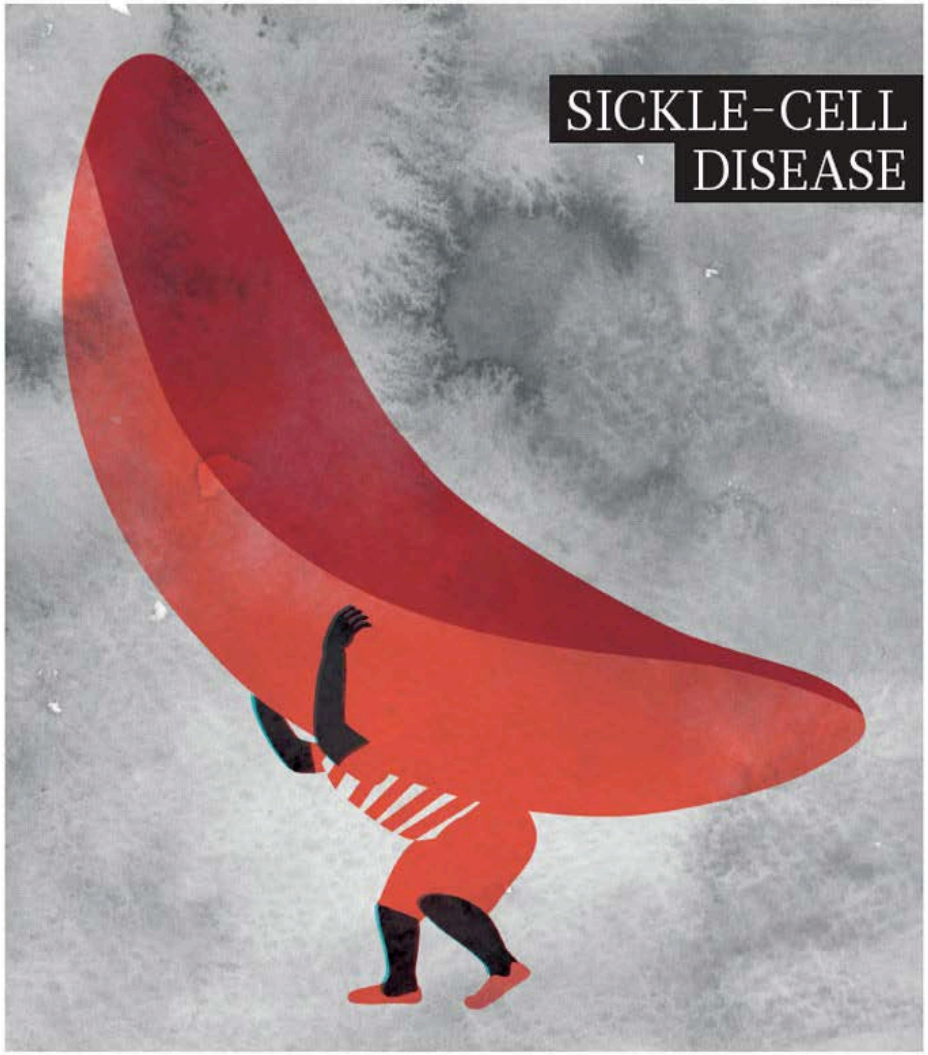
Funding:

NIH

R01 NS040538 (CLS)
R01 NS070711 (CLS)
F31 NS087716 (KJZ)
T32 GM080202 (KJZ)
F31 GM123778 (AMR)

MEDICAL COLLEGE OF WISCONSIN
ADVANCING A HEALTHIER WISCONSIN

nature OUTLOOK

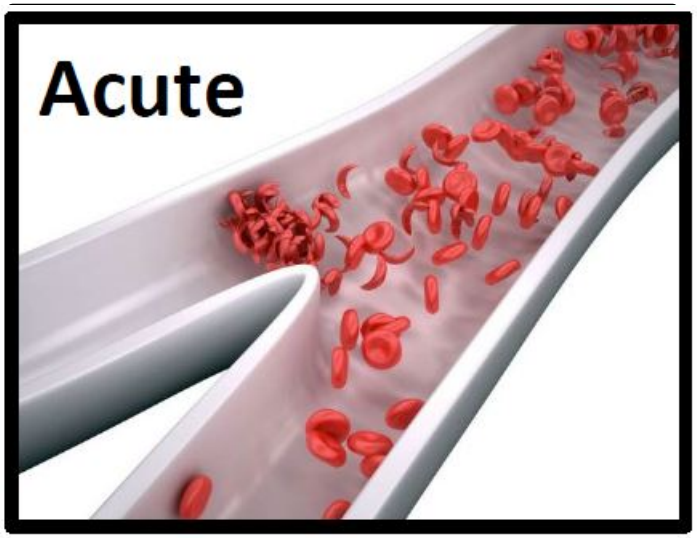


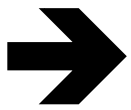
Produced with support from:

Emmaus LIFE SCIENCES, INC.

Steps to ease the burden

Pain in sickle cell disease (SCD)





Chronic

inflammation?

PNS?

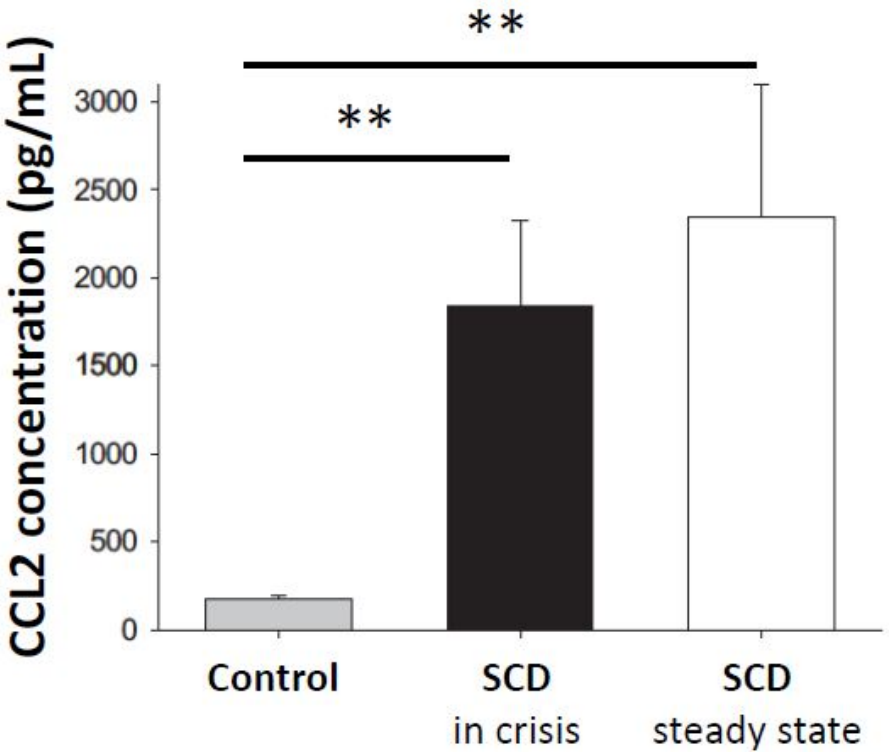
opioid-induced hyperalgesia?

CNS?

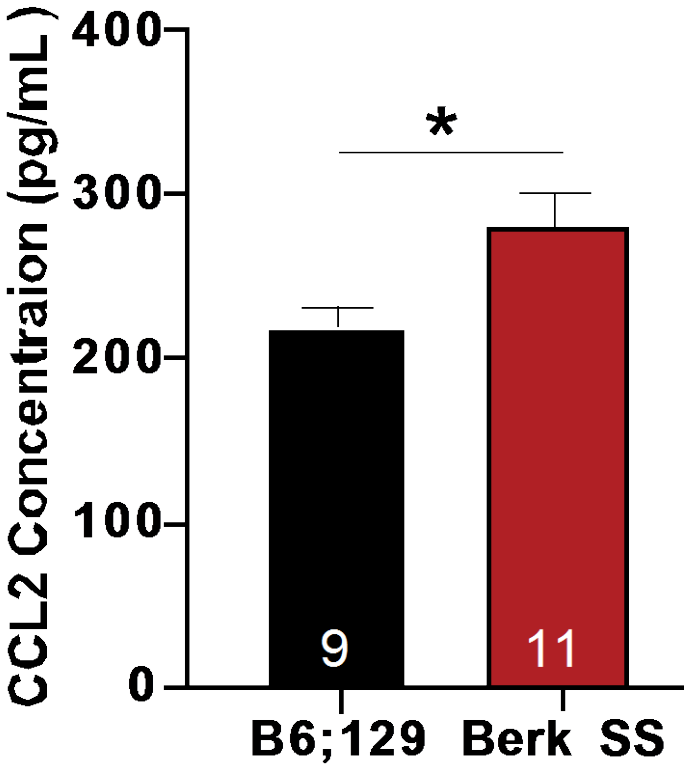
sub-crisis level occlusions?

To what extent do peripheral inflammatory mediators contribute to sickle cell disease hypersensitivities?

CCL2 elevated in SCD patients and mouse models



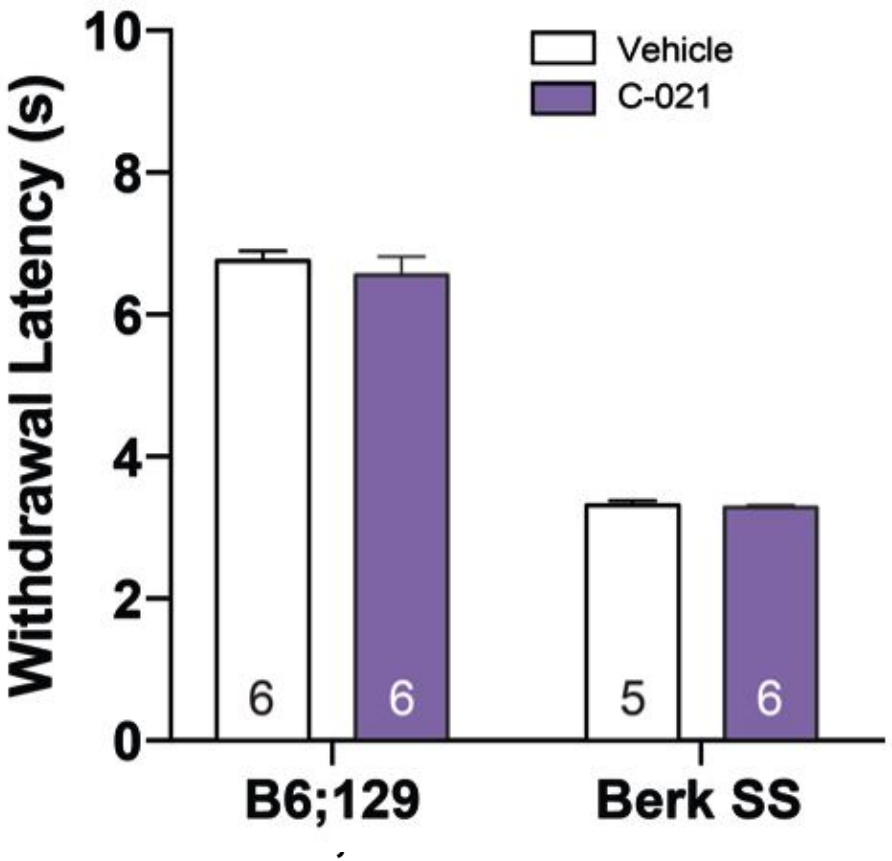
Modified from Quari et al. (2012)
One-way ANOVA: main effect of group ($p<0.05$)
Tukey post-test: **$p<0.01$



Unpaired t-test: *$p<0.05$

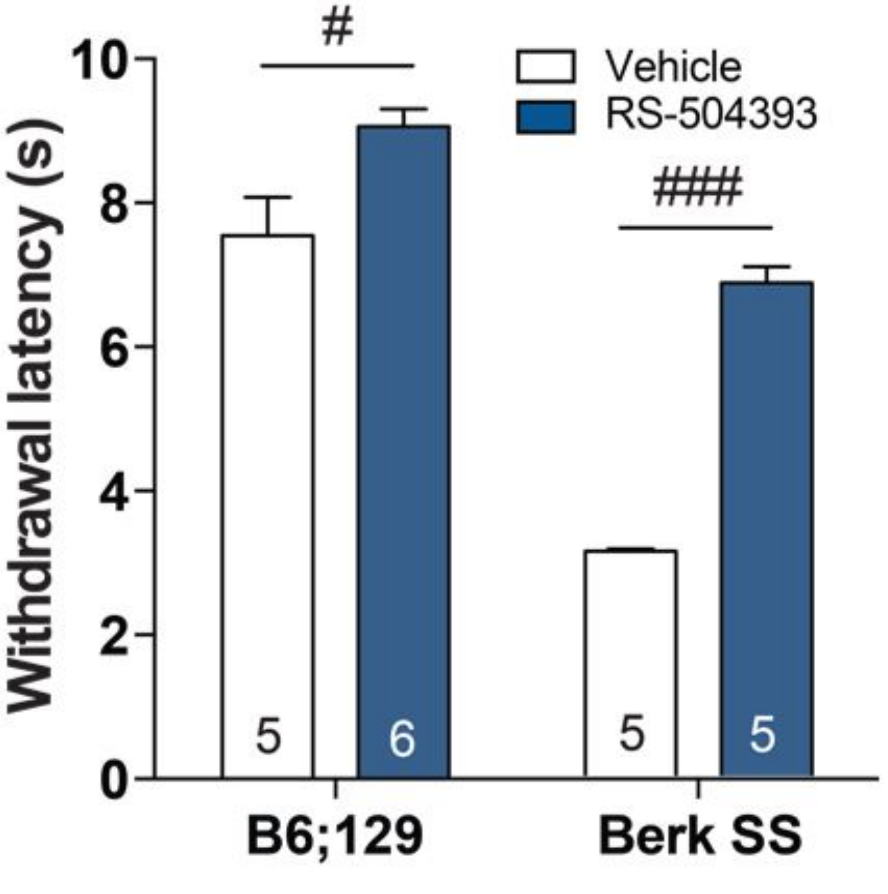
CCR2 signaling mediates cold behavioral sensitivity

CCR4 antagonist



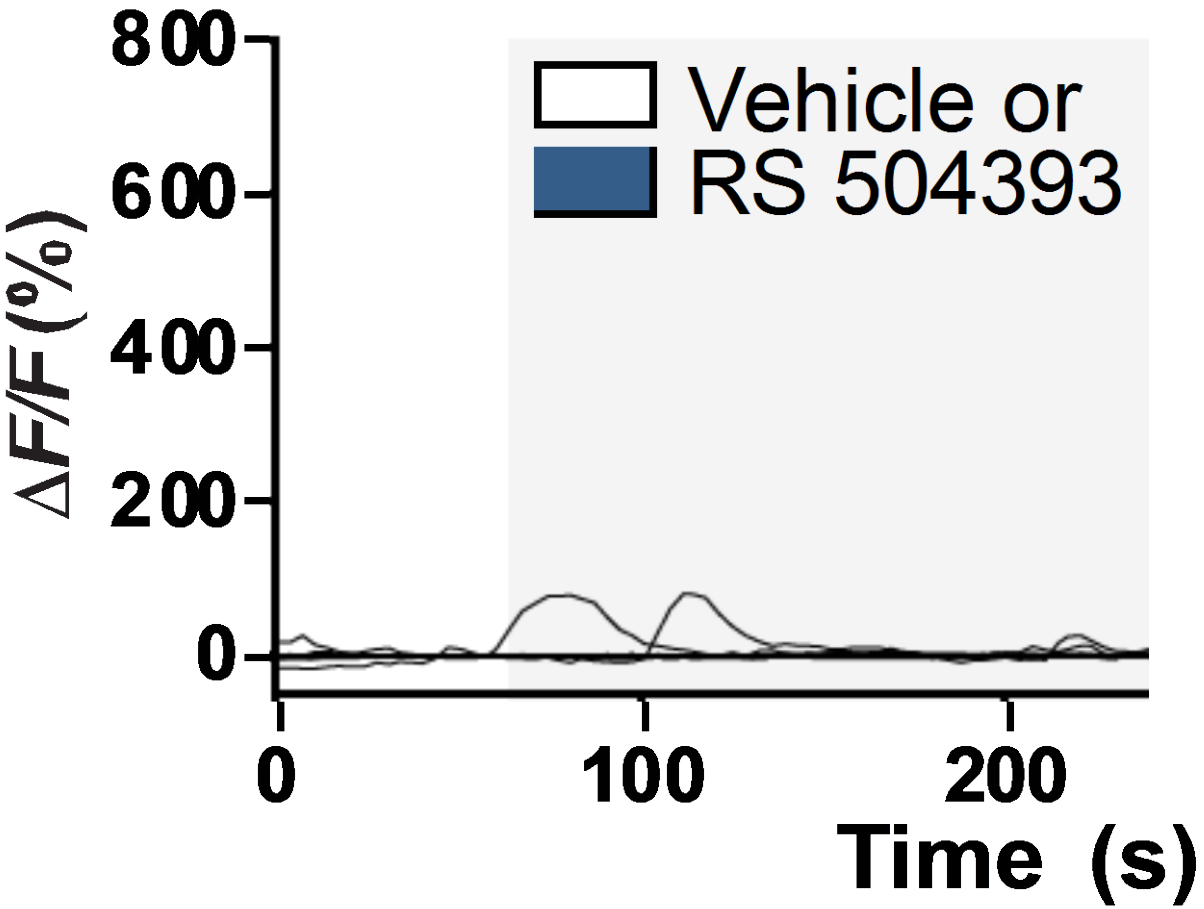
3 mg/kg, s.c.
Two-way ANOVA: effect of genotype ($p<0.05$)

CCR2 antagonist

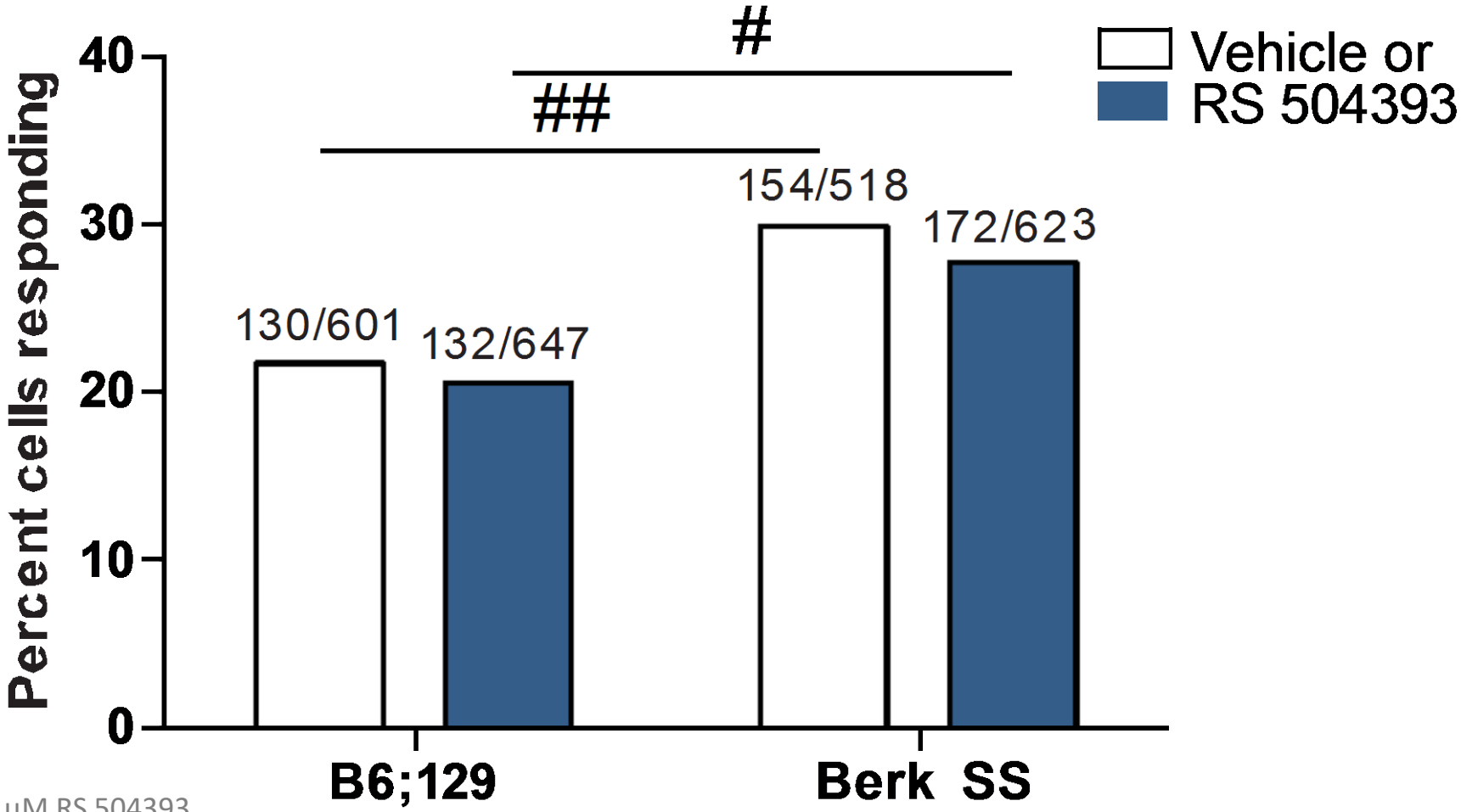


3 mg/kg, s.c.
Two-way ANOVA: effect of genotype ($p<0.05$), drug ($p<0.05$)
Bonferroni post-test: # $p<0.05$, ### $p<0.001$

Assessing contributions of CCR2 to sensory neuron cold sensitivity



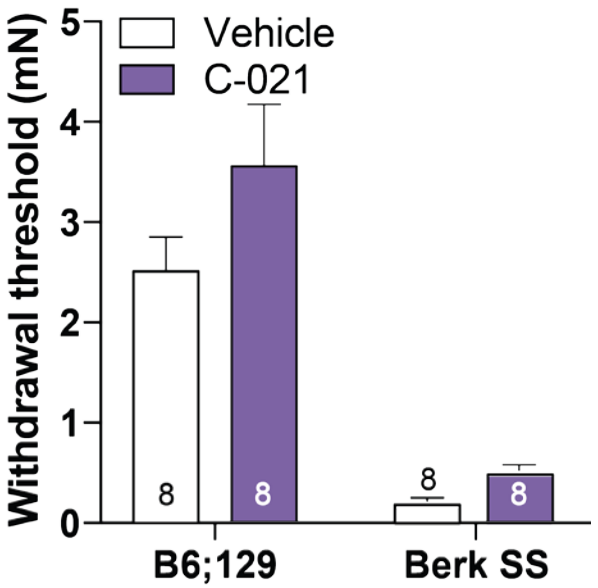
CCR2 does not appear to mediate sensory neuron cold sensitivity



10 µM RS 504393
Two-way ANOVA: effect of genotype ($p<0.05$)
Bonferroni post-test: # $p<0.05$, ## $p<0.01$

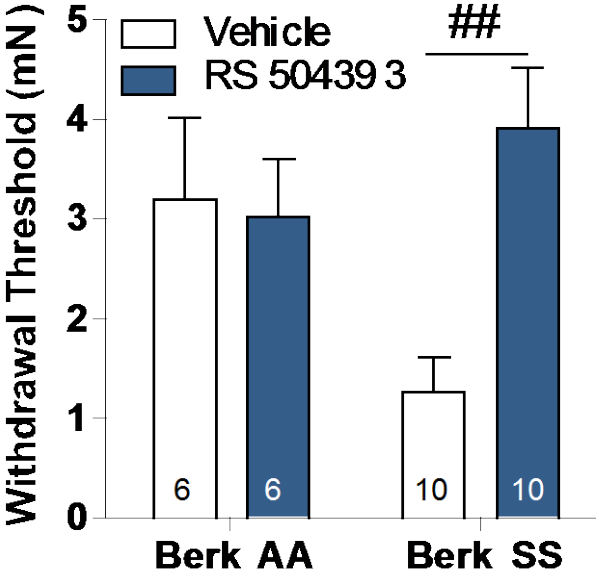
CCR2 signaling mediates mechanical behavioral sensitivity

CCR4 antagonist



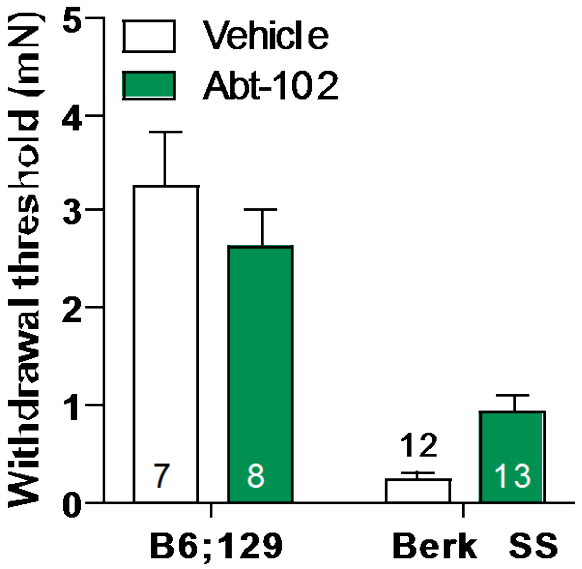
3 mg/kg s.c.
Two-way ANOVA: effect of genotype ($p<0.05$)

CCR2 antagonist



3 mg/kg s.c.
Two-way ANOVA: effect of drug ($p<0.05$), genotype ($p<0.05$)
Bonferroni post-test: ##$p<0.01$

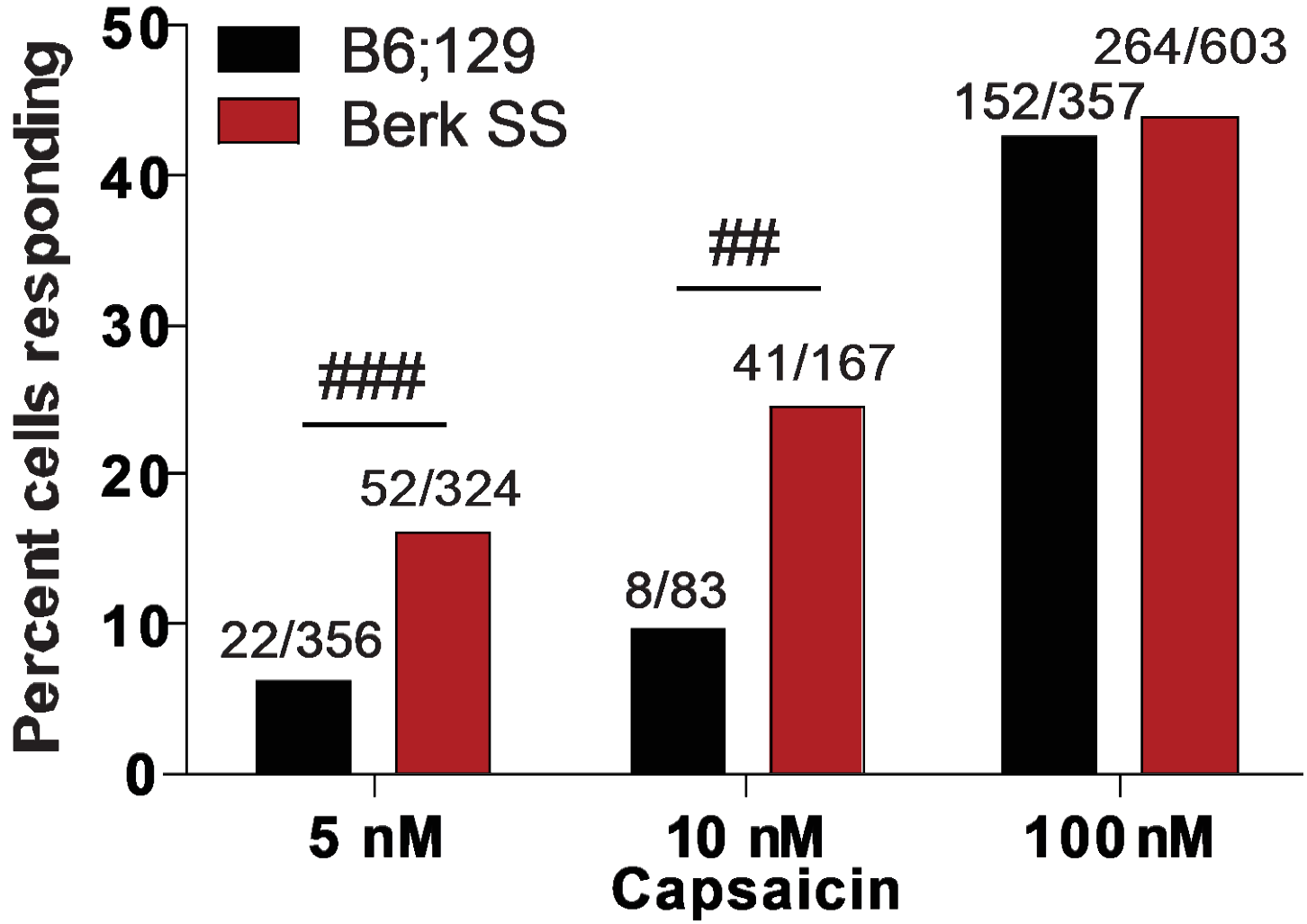
TRPV1 antagonist



10mg/kg i.p.
Two-way ANOVA: effect of interaction ($p<0.05$), genotype ($p<0.05$);

Adapted from Hillery et. al (2011) *Blood*

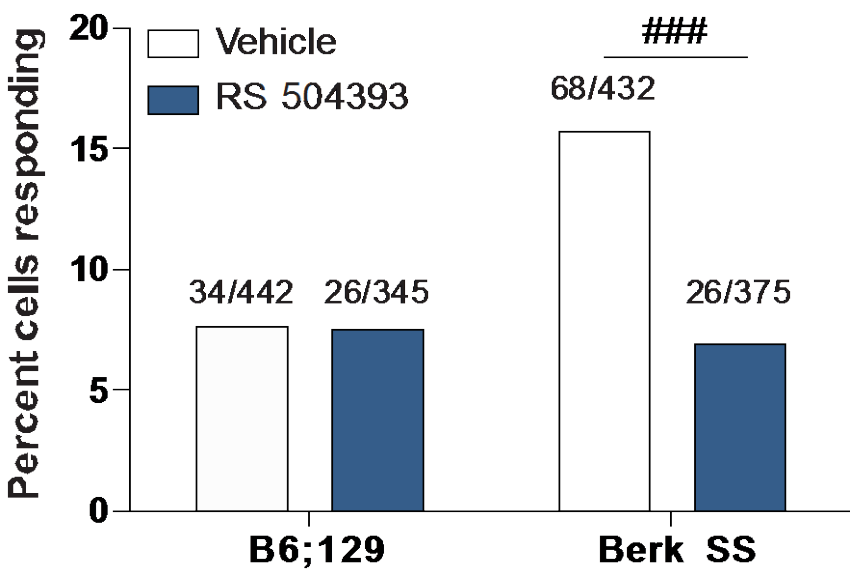
TRPV1 is sensitized in Berk SS neurons



Two-way ANOVA: effect of capsaicin concentration ($p<0.05$), genotype ($p<0.05$)
Bonferroni post-test: ## $p<0.01$, ### $p<0.001$

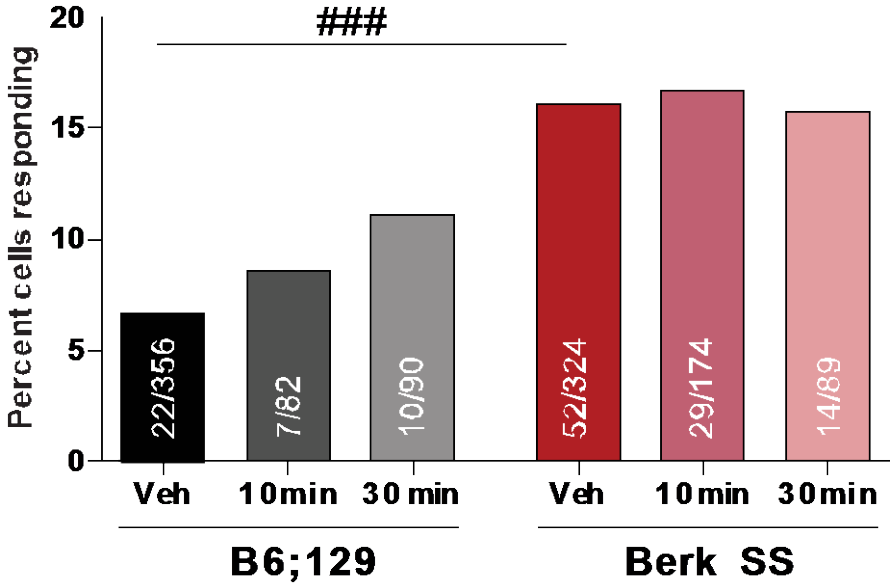
TRPV1 neuronal sensitization is mediated by CCR2

5 nM capsaicin
+ 10 µM CCR2 antagonist



Two-way ANOVA: effect of genotype ($p<0.05$)
Bonferroni post-test: ### $p<0.001$

5 nM capsaicin
+ 100 nM CCL2



Two-way ANOVA: effect of genotype ($p<0.05$)
Bonferroni post-test: ### $p<0.001$

CCR2 Signaling Mediates:

Cold behavior sensitivity

Mechanical behavior and neuronal sensitivity (TRPV1-dependent)

Future direction: CCR2/TRPV1 coupling mechanism