Integrative Approaches to Combat Pain: What Can We Do?

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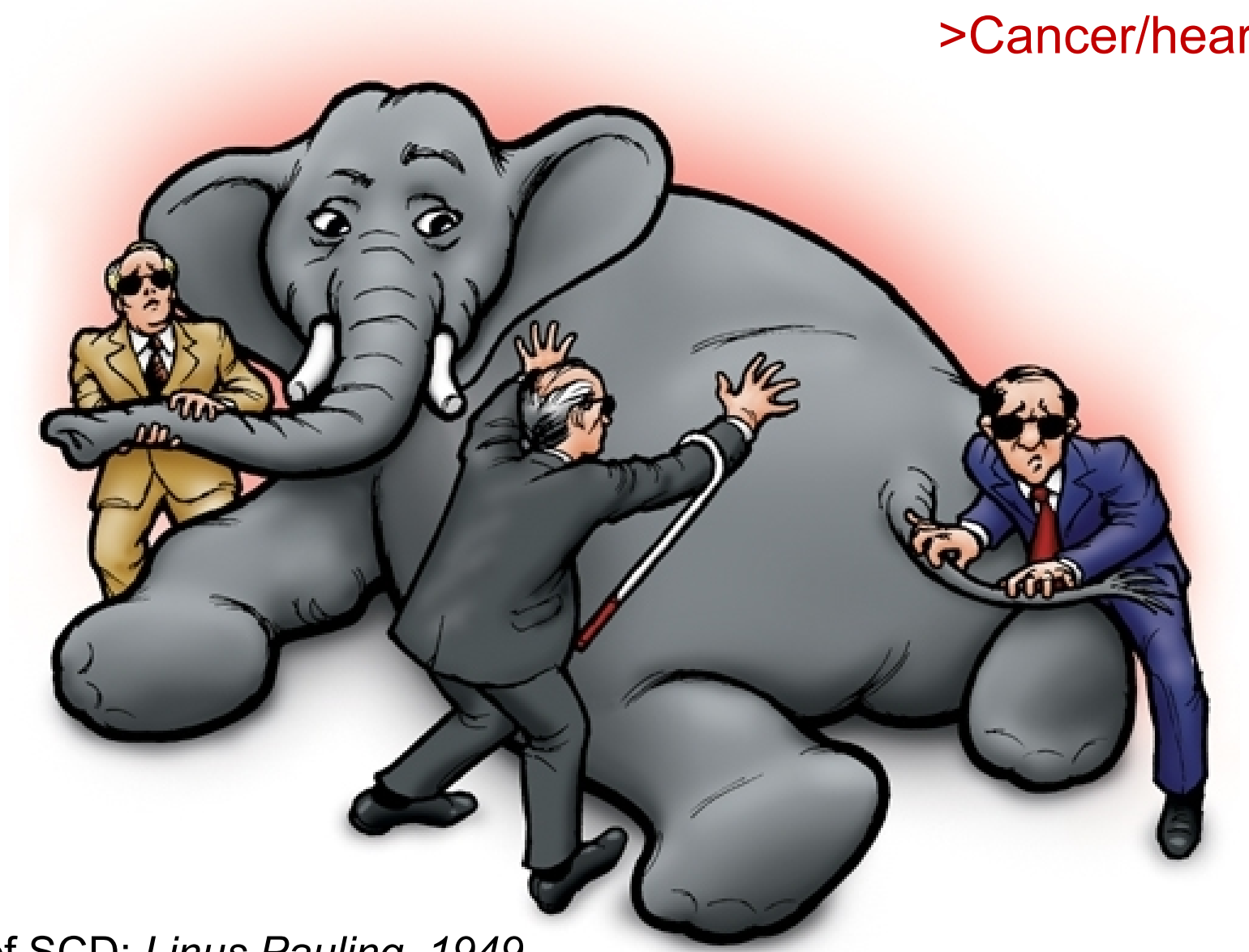
What is Pain?

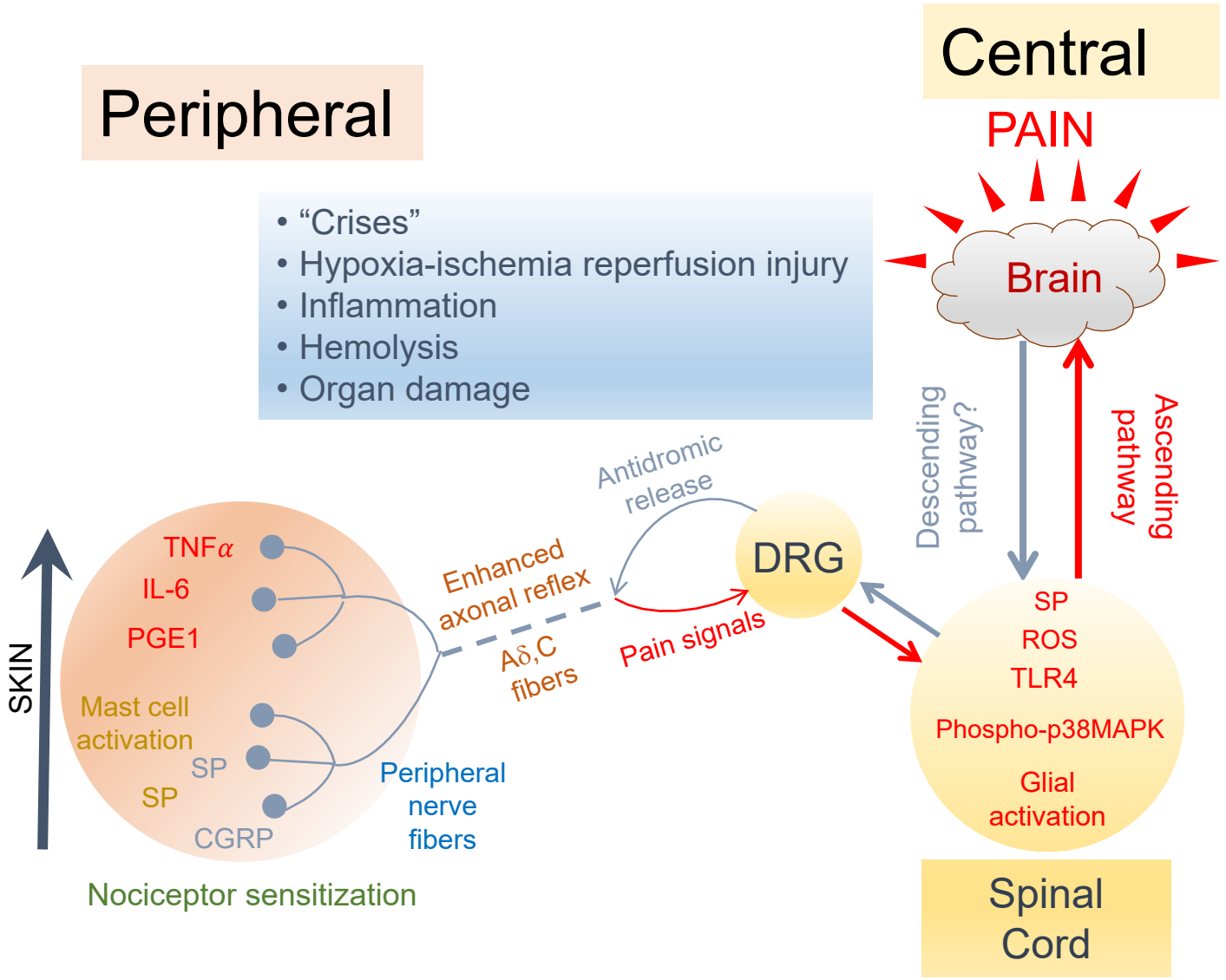
Pain: $635 billion/year
>Cancer/heart disease/diabetes



Molecular basis of SCD: *Linus Pauling, 1949*
Pain in SCD: A scientific enigma, 2022?

Annual Cost of hospitalization for SCD, USA: $488 million

What causes pain in sickle cell disease?



Aich A, Beitz A & Gupta K, 2016. In, Sickle Cell Disease, Inusa B (Ed)

Alternative, Complementary and Integrative Medicine

- A combination of *medical* and *complementary* therapies.
- Based on scientific evidence.
- *Complementary*: Non-conventional therapy used with traditional medicine
- *Alternative* and *complementary* used interchangeably.
- *Alternative*: Used in place of traditional medicine

Can diet influence pain in SCD?

Tx with 0.25 g/Kg fish oil for 1-year significantly reduced frequency of pain events to ~50% Vs previous year or placebo (olive oil) in 10 persons with SCD.
Emory University, Atlanta, GA.
(*Tomer, Kasey, Connor, Clark, Harker, Eckman Throm Hemostas 2001*).

Omega-3 capsules (277.8 mg DHA + 39.0 mg EPA) for 1 year significantly reduced median rate of clinical vasocclusive events, anemia, WBC counts and blood transfusion in 140 SS subjects.
Khartoum, Sudan.
(*Daak, et al., Am J Clin Nutr 2013*)

CoQ10 reduces inflammation and oxidative stress in trait and homozygous SCD

Hematological Parameters and RBC TBARS Level of Q 10 Supplemented Tribal Sickle Cell Patients: A Hospital Based Study
Ind J Clin Biochem (Apr-June 2013) 28(2):185–188
S. Thakur • G. P. Littaru • S. Moesgaard • C. Dan sindberg • Y. Khan • C. M. Singh.
Jagdalpur, Chattisgarh, India

Control (20) Trait (19) and homozygous (15) patients: 10 -55 years
200 mg CoQ10 per day for 6 months

Significant decrease in CRP (inflammation) and TBARS (lipid peroxidation) in AS and SS patients

High protein diet since weaning attenuates organ damage

High protein diet attenuates histopathologic organ damage and vascular leakage in transgenic murine model of sickle cell anemia

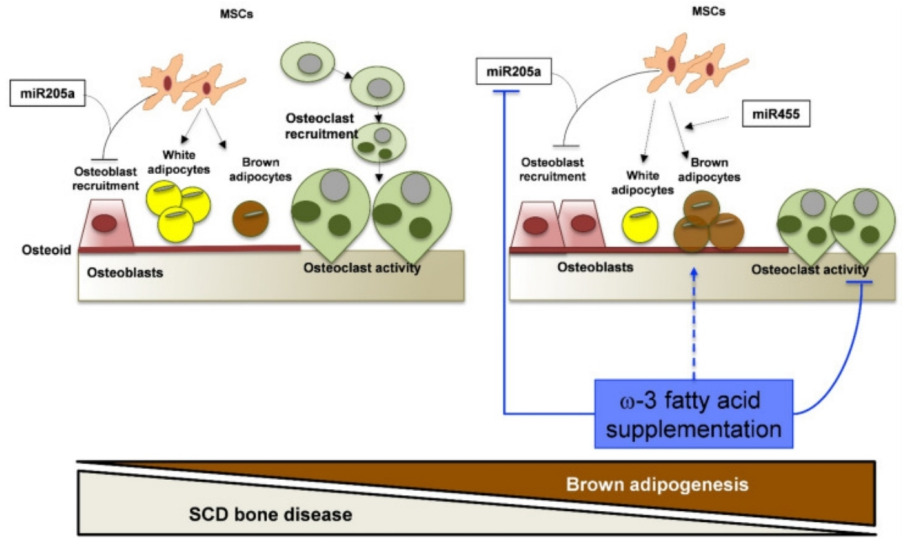
Elizabeth Ann Manci, Hyacinth I Hyacinth, Patrice L Capers, David R Archer, Sydney Pitts, Samit Ghosh, John Patrickson, Michael E Titford, Solomon F Ofori-Acquah, and Jacqueline M Hibbert

Exp Biol Med (Maywood). 2014 August ; 239(8): 966–974.

Dietary ω-3 Fatty Acid Supplementation Improves Murine Sickle Cell Bone Disease and Reprograms Adipogenesis

Maria Teresa Valenti,[1,†] Alessandro Mattè,[1] Enrica Federti,[1] Mark Puder,[2] Lorenzo Anez-Bustillos,[2] Michela Deiana,[1] Samuele Cheri,[1] Arianna Minoia,[1] Carlo Brugnara,[3] Maria Luisa Di Paolo,[4] Luca Dalle Carbonare,[1,*†] and Lucia De Franceschi[1,†]

Antioxidants (Basel). 2021 May; 10(5): 799.
Published online 2021 May 18. doi: 10.3390/antiox10050799



Fish oil based dietary (FD) supplementation (omega 3 fatty acids) ameliorate sickle cell bone disease. FD supplementation reduces osteoclastogenesis/osteoclast activity and downregulates miR205a, favoring osteoblastogenesis/activity. Finally, FD re-programing of adipogenesis resulted in the browning of white adipocyte tissue. The multimodal action of FD protects bone from sickle cell related tissue damage. SCD: sickle cell disease; MSC; mesenchymal stem cells.

Humanized Transgenic Berkeley (BERK) Mice Expressing Human Sickle Hemoglobin Recapitulate Many Features of SCD

Hba^{tm1Paz} Hbb^{tm1Tow} Tg(HBA-HBBs)41Paz/J

- Homozygous mice express >99% human sickle hemoglobin
  - Homozygous knockout of murine alpha- and beta-globin
  - Transgenic expression of human alpha- and beta sickle-globin (*Paszty et al., Science 1997)*
- Express many hematological and pathological features of SCD
- Develop chronic mechanical, thermal and musculoskeletal hyperalgesia at 3.0-3.5 months of age (*Kohli et al., Blood 2010*)

Improved Dietary Components in Sickle Diet

		Rodent Diet	Sickle Diet
Minerals	Magnesium	0.2%	0.48 %
	Zinc	70 ppm	225 ppm
	Copper	15 ppm	30 ppm
Amino Acids	Arginine	1%	2.52 %
	Cystine	0.4%	0.7%
	Aspartic Acid	1.4%	2.53 %
	Glutamic Acid	3.4%	5.16 %

		Rodent Diet	Sickle Diet
Vitamins	Vitamin A	15 IU/g	33 IU/g
	Vitamin E	110 IU/g	200 IU/g
	Folate	4ppm	8ppm
	Vitamin B-12	0.08 mcg/kg	60 mcg/kg
Fatty Acids	Omega-3 fatty acids	0%	0.26%
Energy density		Protein: 24% Fat: 18%	Protein: 27.5% Fat: 26%

Diet and Companionship modulate pain in sickle mice

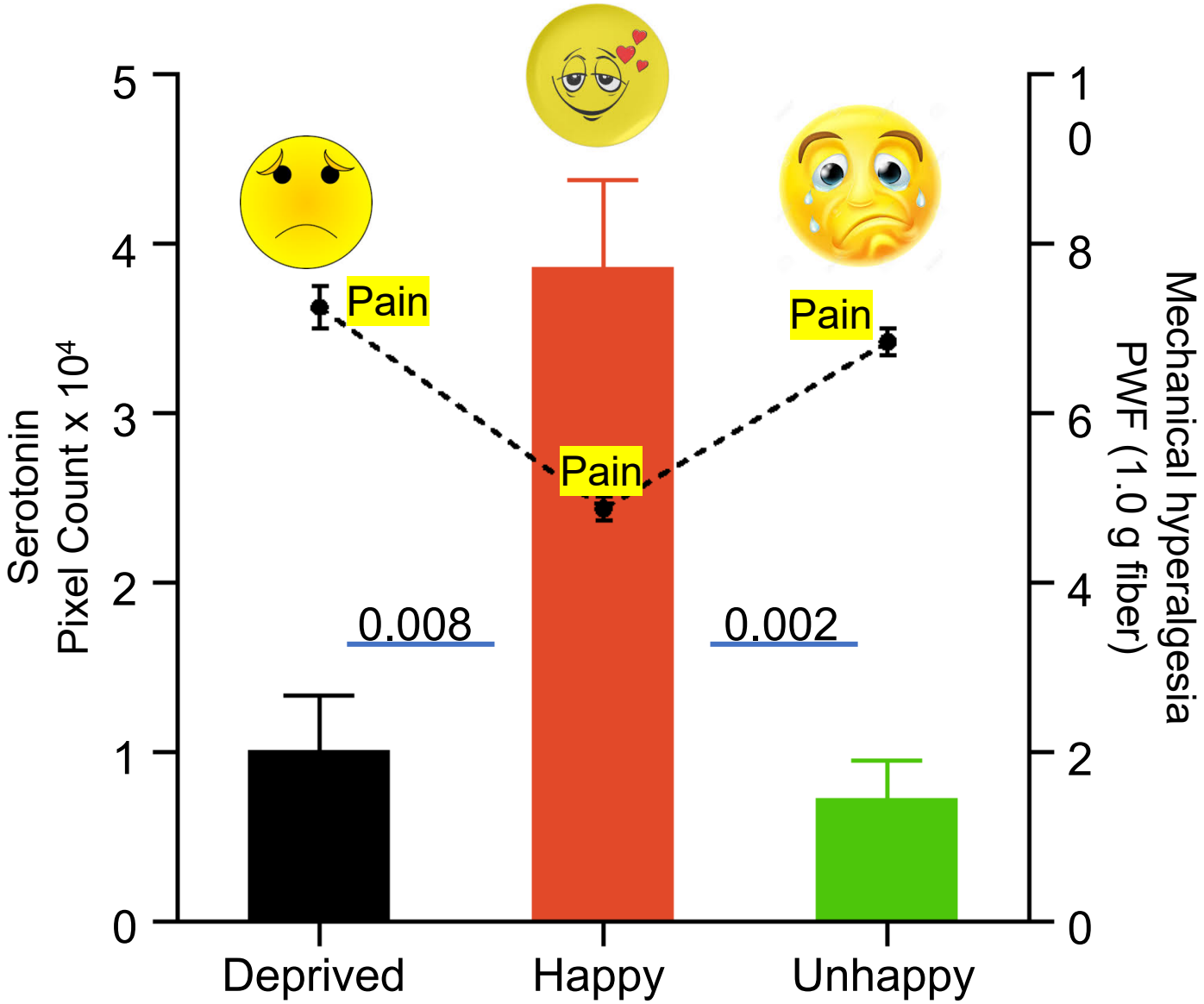
Tran H, Sagi V, Jarrett S, Palzer EF, Badgaiyan RD, Gupta K. Sci Rep. 2021 Feb 1;11(1):2330.

Deprived	Happy
Male in isolation on Rodent Diet without companion (RD/M-)	Male on Sickle Diet with female companion [SD/M+]
	Unhappy Withdrawal of happiness Female withdrawn leaving the male mouse alone

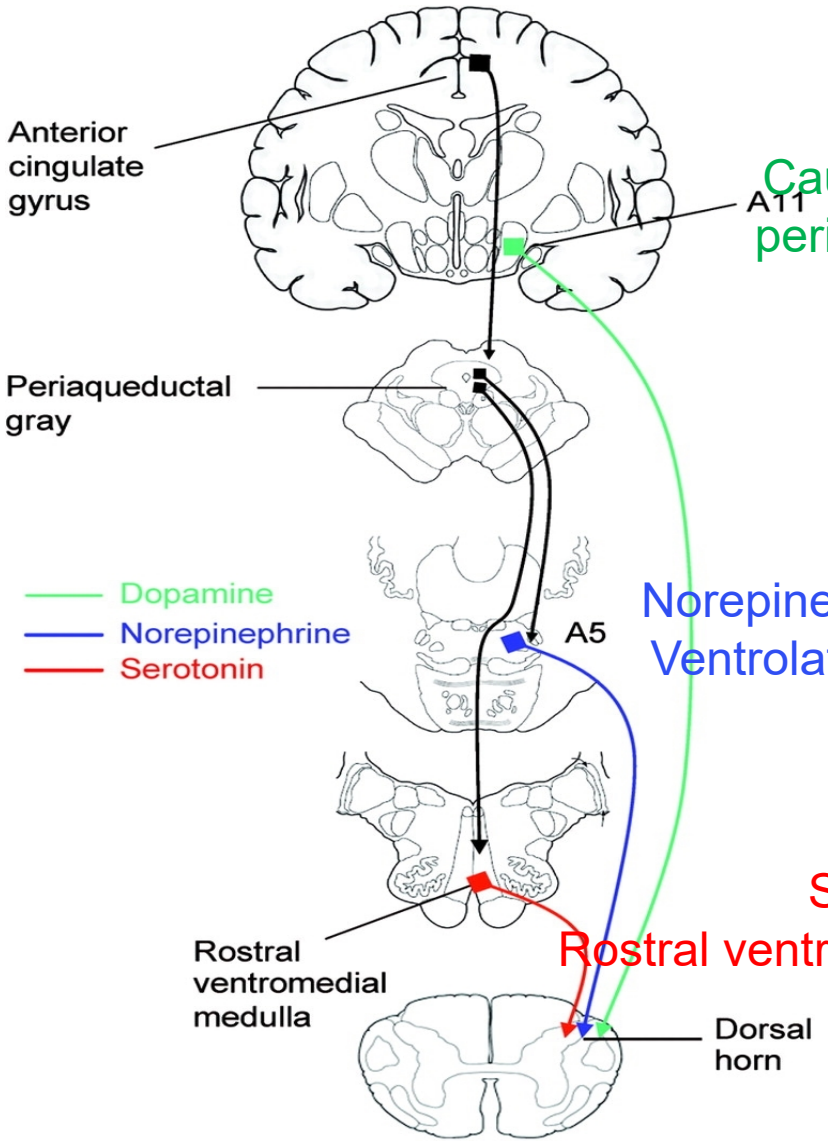
Treatment groups: (n=10/treatment), HbSS-BERK

Dr Huy Tran
Resident
Univ Arkansas

Diet and companionship reduce pain



Spinothalamic mechanisms mediate pleasure-related analgesia.

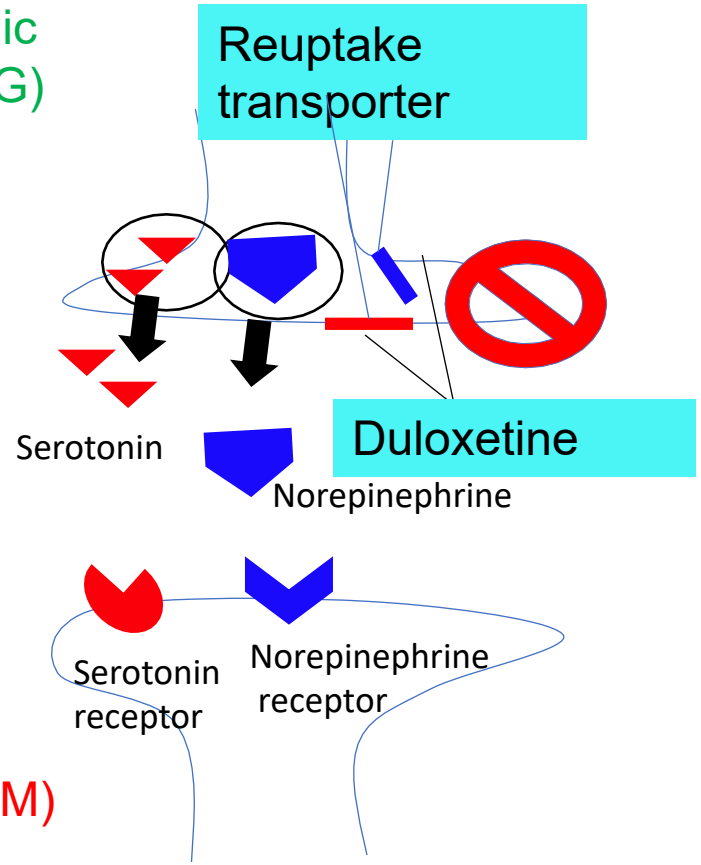


Dopaminergic
Caudal mesodiancephalic periaqueductal grey (PAG)

Norepinephrinergic
Ventrolateral pons

Serotonergic
Rostral ventromedial medulla (RVM)

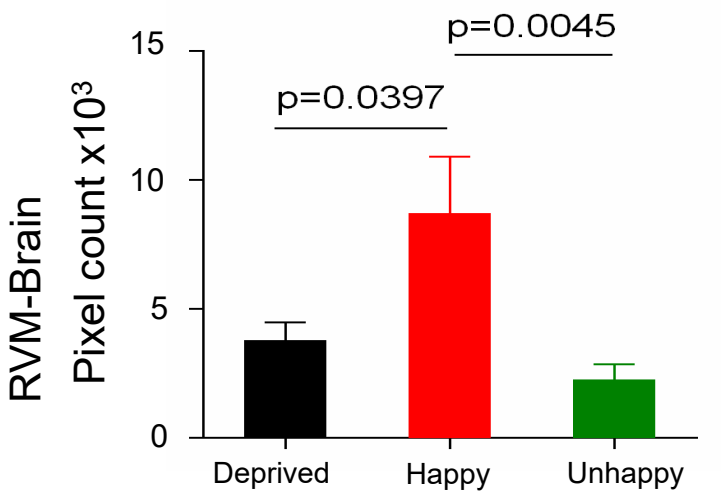
Serotonergic and norepinephrinergic neurons

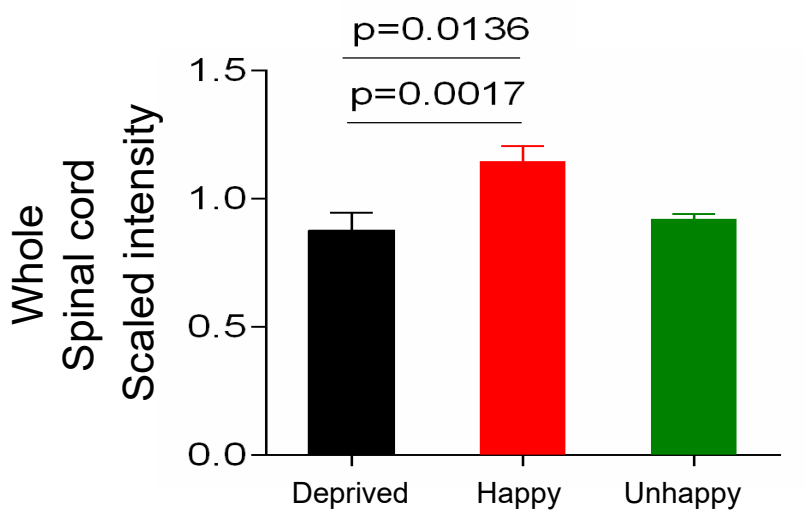


First and second order nerve terminals

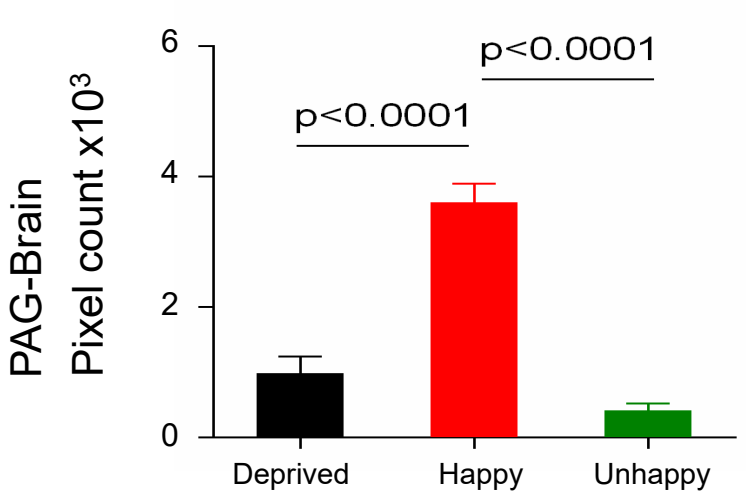
Withdrawal of pleasure diminishes spinothalamic anti-nociceptive mechanisms.

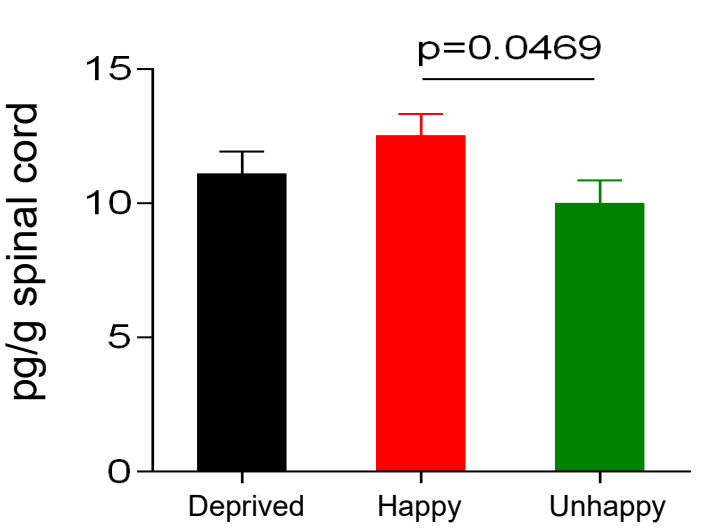
Serotonin





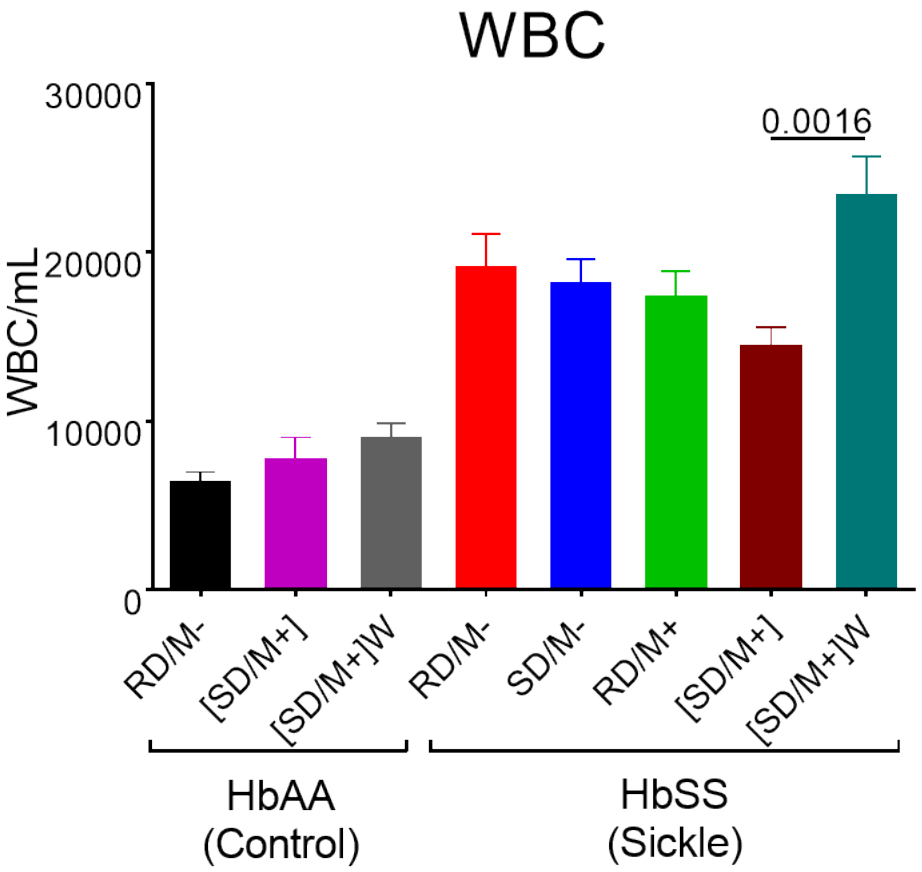
Dopamine

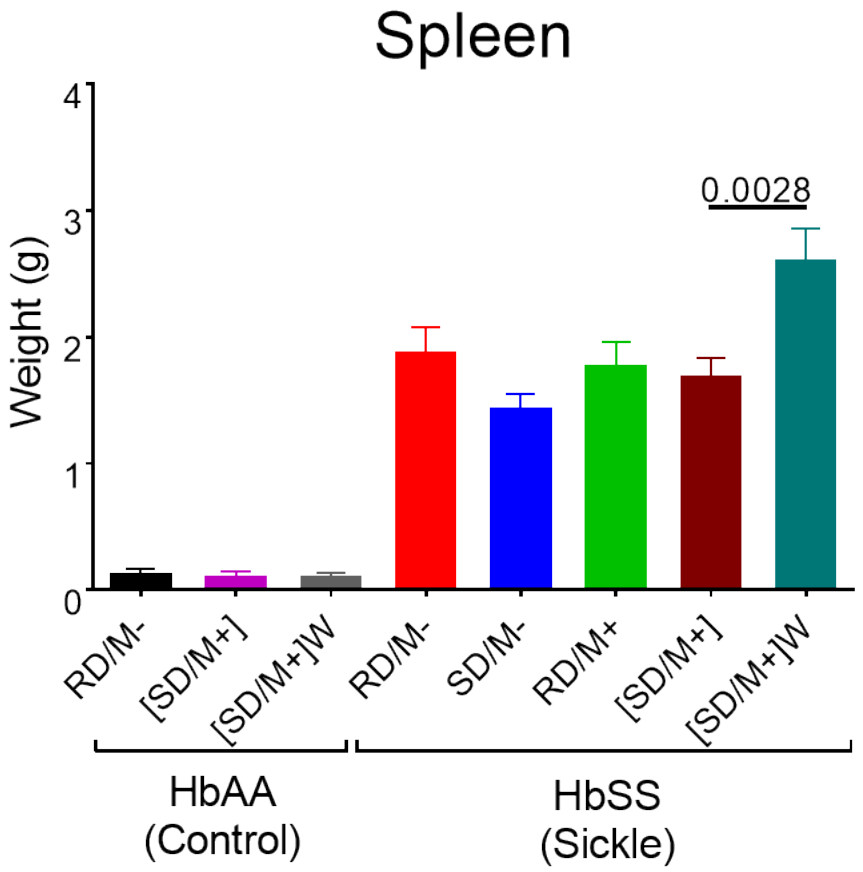




Male HbSS-BERK; n=6

Withdrawal of high calorie diet and mating increases inflammation and splenomegaly.

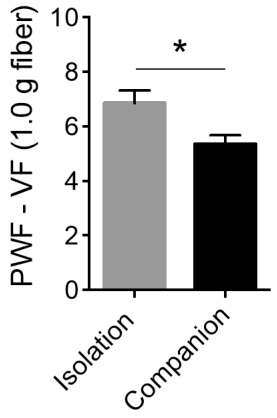




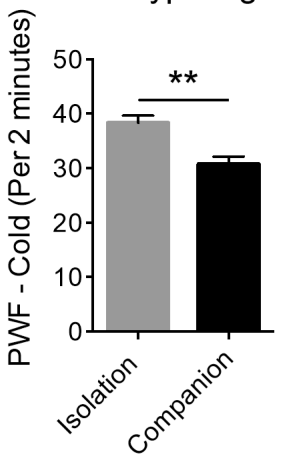
~8-10 mo male HbSS BERK

Isolation increases nociception in male sickle mice

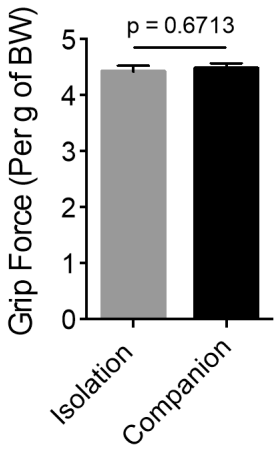
Mechanical Hyperalgesia



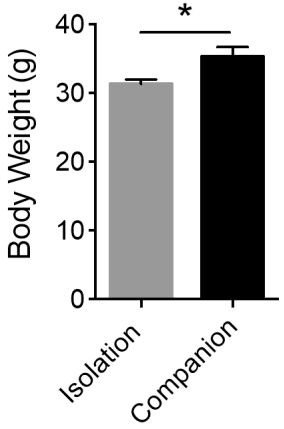
Cold Hyperalgesia



Deep Hyperalgesia



Body Weight

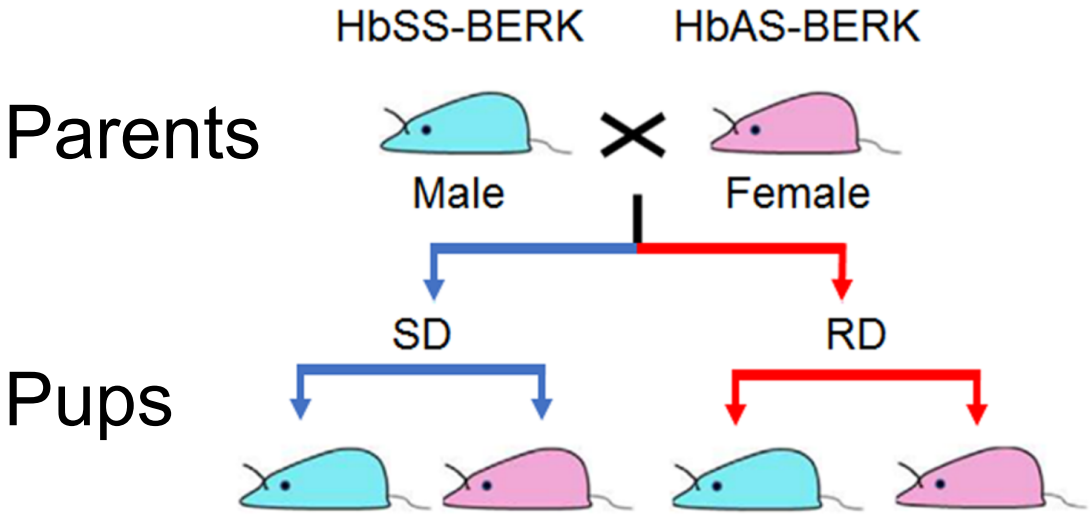


Stacy Kiven
→ Georgetown University

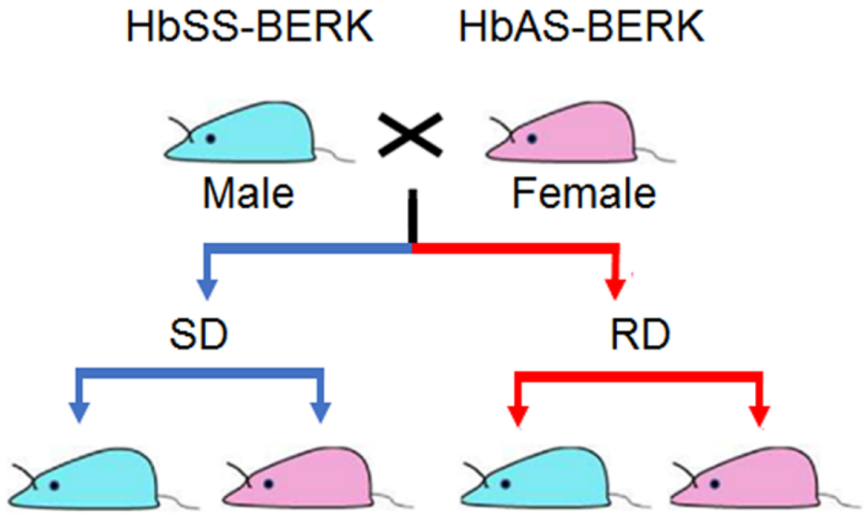
Male HbSS BERK mice n = 16 per group. Avg. age Isolation group = 18.9 months, companion = 16.2 months. Abbreviations: BW, Body Weight; PWF, paw withdrawal frequency Data shown as mean +/- SEM. Analyzed with student's T-test. * p< 0.05, ** p<0.001.

Intervention can begin before birth

Regular Rodent diet (RD)



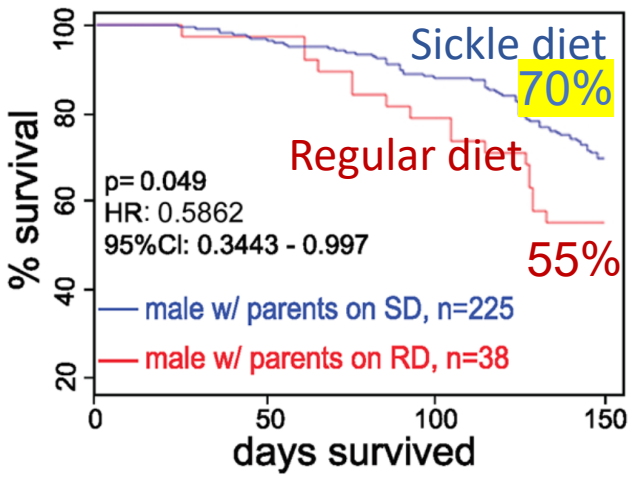
High Protein/Fat Sickle diet (SD)



Jahagirdar et al., Haematologica 2019

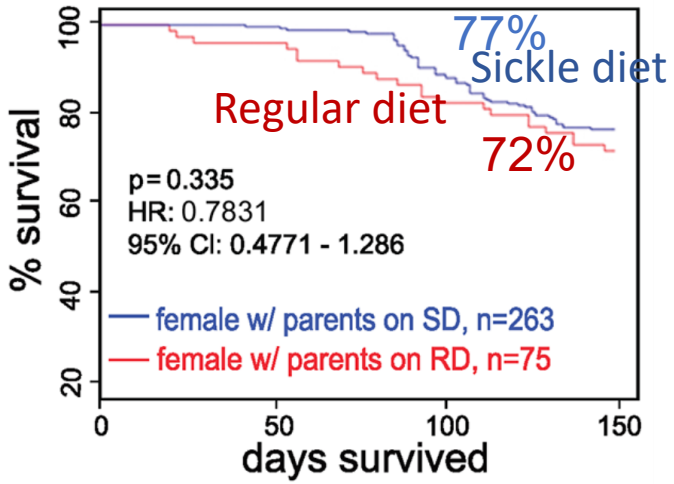
Parent's as well as offsprings' diet influences survival of sickle mice

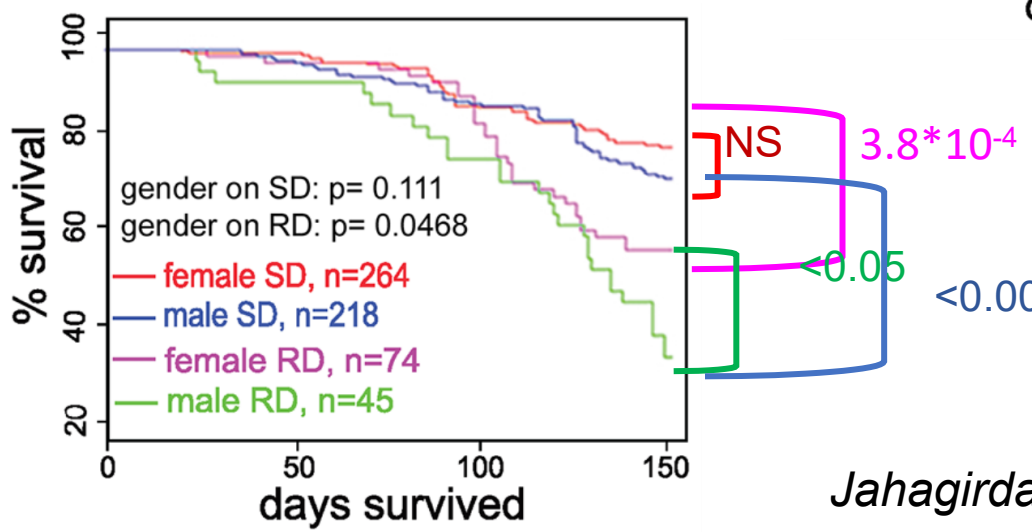
Male offsprings



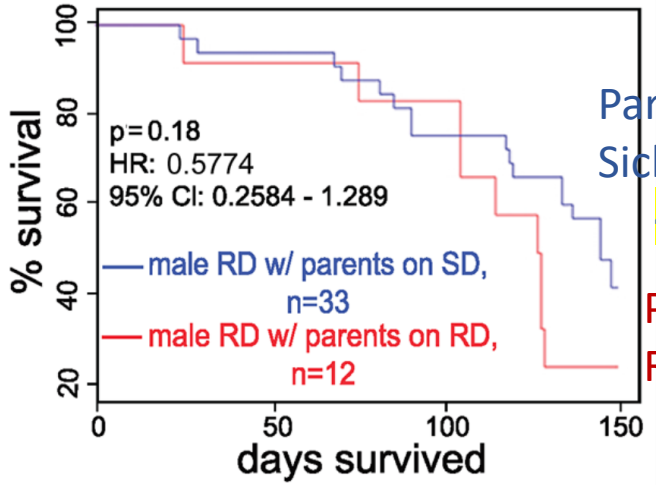
Om Jahagirdar
Stanford University

Female offsprings





Male offsprings on regular diet from parents on regular Vs sickle diet



Parents on Sickle diet
42%

Parents on Regular diet
25%

Mouse age, 5 month
= Human age, ~30 yrs

Jahagirdar et al., Haematologica 2019

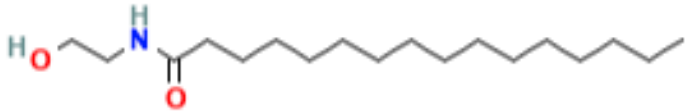
Maternal Dietary Intakes, Red Blood Cell Indices and Risk for Anemia in the First, Second and Third Trimesters of Pregnancy and at Predelivery.

Agbozo F, Abubakari A, Der J, Jahn A. Nutrients. 2020 Mar 15;12(3):777.

“Overall, adolescence, poor diet, suboptimum antenatal care and underweight were associated with moderate and severe anemia. In specific time-points, dietary counselling, malaria, iron-folic acid supplementation, sickle cell disease and preeclampsia were observed.”

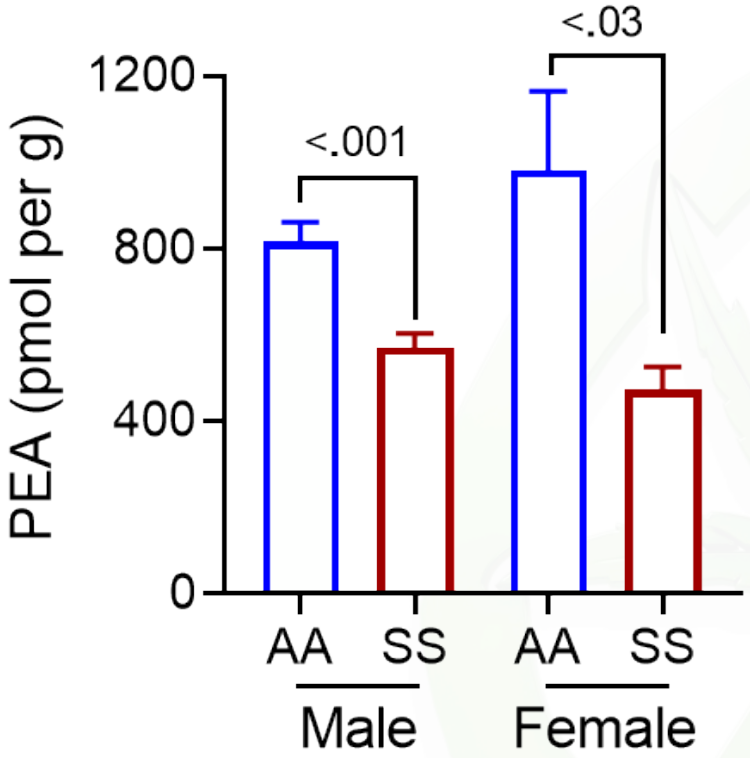
Spinal Cord Palmitoylethanolamide is Significantly Reduced in Male and Female Sickle Mice

Palmitoylethanolamide (PEA)



- PEA is a lipid mediator with described anti-inflammatory, neuroprotective and analgesic effects in clinical & pre-clinical studies
- *Was discovered in Italy in egg yolks and also synthesized endogenously by the body*

Measured using Ultra-Performance Liquid Chromatography Tandem Mass Spectrometry (UPLC-MS/MS)
[Sub nanomolar resolution]

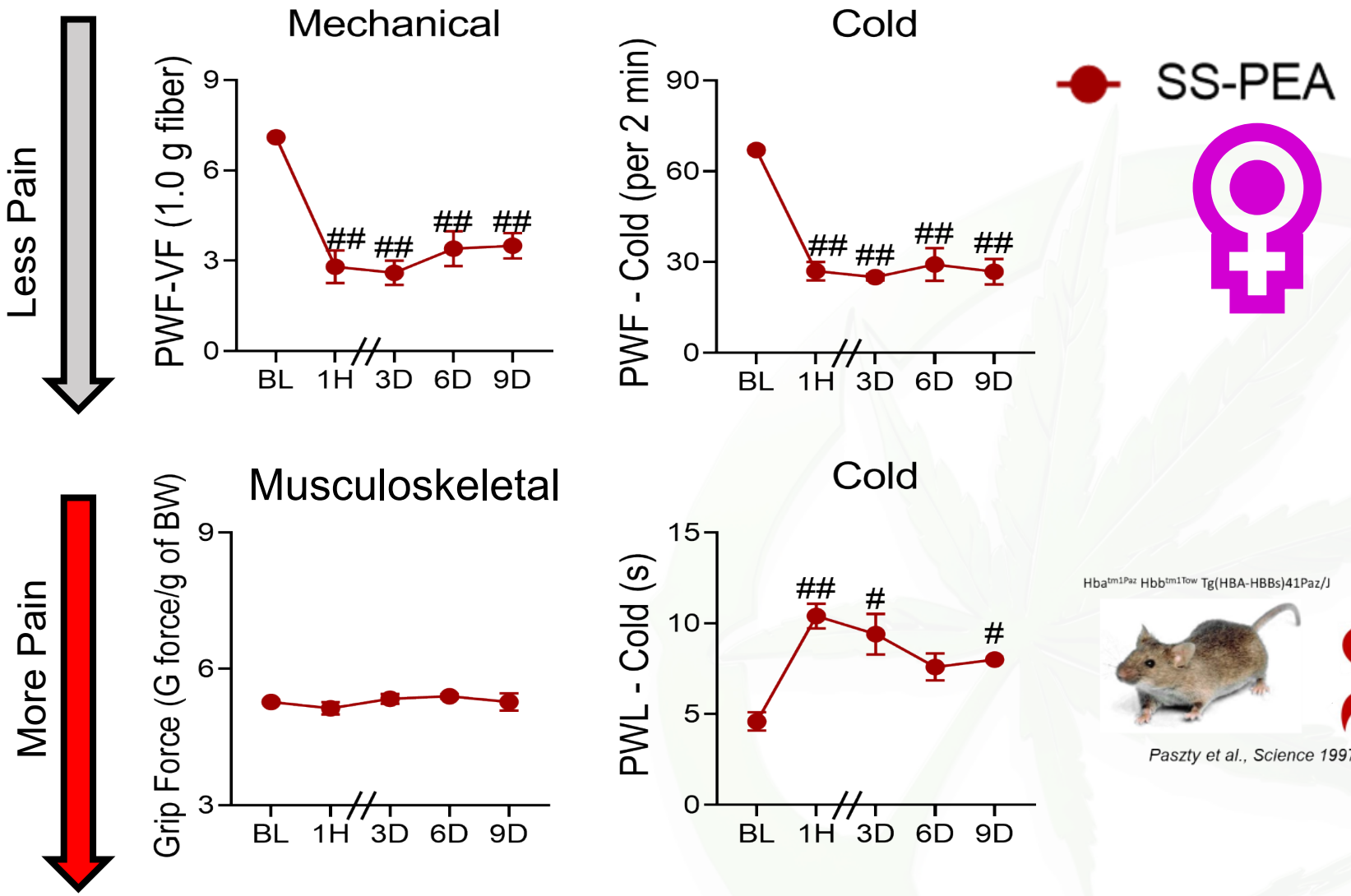


Age: 3.5-5 Months

mean ± SEM, N=6-10. Two-Tailed T-test

Donovan Argueta, PhD
University of California
President's Post-doctoral
Fellow and
Giannini Foundation Fellow

Chronic Treatment with PEA Attenuates Hyperalgesia



Female, 3.5-4.5 Months. PEA (i.p., 20 mg/kg/d). Data shown as mean ± SEM. N=5; two-way ANOVA, Tukey's post hoc test. **#** indicates significant difference compared to BL. **#** - $p<0.05$; **##** - $p<0.01$. BL - baseline, PWF - paw withdrawal frequency, PWL - paw withdrawal latency, VF - Von Frey

Affective modulation influences opioid analgesia in SCD

- Lower dose of morphine is required to reduce pain in happy sickle mice.

"High symptom burden and depression in patients on chronic opioid therapy"

Chronic opioid therapy and central sensitization in sickle cell disease
Carroll CP et al., *Am J Prev Med* 2016;51(Suppl):S69-77.

"Pain and pain-related cognitive and affective variables are associated with daily variation in opioid use in SCD."

Daily opioid use fluctuates as a function of pain, catastrophizing, and affect in patients with SCD: an electronic daily diary analysis
Finan PH, et al. *J Pain* 2017.

Conclusion: Nutrition, relationships, emotional stability & environment to improve well-being

Maternal health is important: Early and pre-natal dietary interventions can improve SCD pathobiology and survival.

Environment: Diet and life-style (companionship/pleasure), emotional well-being may be helpful in ameliorating pain, reducing opioid requirement and improving survival in SCD.

Perception-based interventions: Virtual reality, mind-body practices, hypnotism and perception-based imagery may be useful in reducing pain and opioid requirement.

Share the burden and eat healthy

Google images; NY Times.com

Google images; Hope.School

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UCI Susan Samueli Integrative Health Institute (SSIHI) – Integrative Clinical Care

AMBULATORY CARE

- UCI SSIHI offers Integrative health services at 7 clinics throughout UCI Health
- Over 18,000 integrative health visits

INPATIENT CARE

UCI SSIHI operates an inpatient acupuncture program at UCI Medical Center

- Indications include pain, sleep, anxiety or nausea
- Over 5,400 patients treated
- Improvements in symptoms
- Lower opioid use
- Lower 30-day readmission

HEALTH ENTERPRISE INTEGRATION

UCI SSIHI launched integrative nursing initiative in early 2020 which allows inpatient nurses to obtain training in integrative health modalities

- Over 95% of UCI Health nurses have been trained
- Over 7,500 interventions
- Improvements in symptoms compared to usual care
- Lower opioid use
- Lower 30-day readmission

COMMUNITY CARE

The UCI SSIHI partners with FQHC and community clinics to provide integrative health care.

- Acupuncture, nutrition education, group visits, lifestyle medicine

UCI Susan Samueli Integrative Health Institute

Thank You!

Danke!

धन्यवाद

Shukraan!　ありがとうございました!

謝謝

teşekkür ederim

Dank je!

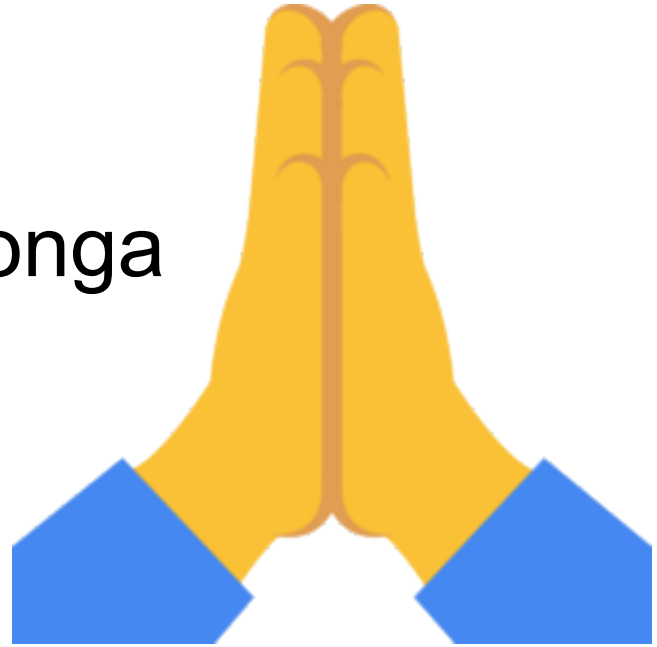
ඔබට ස්තුතියි

ua tsaug rau koj!

Asante

תודה רבה לך

Ngiyabonga



Je vous remercie!

gracias