EFFECTS OF A KETOGENIC DIET ON PAIN TOLERANCE AND TACTILE SENSITIVITY ACROSS THE ESTROUS CYCLE IN FEMALE RATS

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INTRODUCTION

A Ketogenic Diet

- High fat, sufficient protein, extremely low carbohydrate diet that induces a metabolic state of ketosis
- Glucose metabolism is minimized, ketone bodies become primary cellular fuel source
- Most notably used to treat epilepsy

Antiepileptic Mechanisms

- Restriction of glucose metabolism is thought to induce cellular changes which decrease neuronal excitability
- Increased levels of adenosine → increased activation of adenosine A_1 receptors[1]
- Enhanced GABAergic neuronal inhibition[2]

Potential Antinociceptive Effects

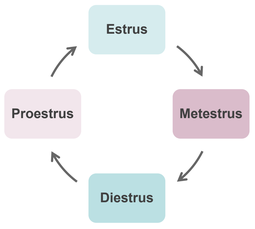
- Anticonvulsant medication used to treat neuropathic pain[3]
- Adenosine A_1 receptor activation decreases tactile sensitivity and pain sensitivity in mice[4]
- GABA signaling decreases nociception[5]

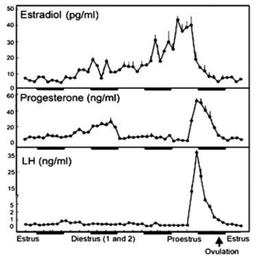
Potential as a Treatment for Chronic Pain

- Current chronic pain treatments offer poor long-term efficacy[6]
- KD administration decreases tactile hypersensitivity and thermal pain sensitivity in male rats[7]

Sex Hormones and Pain Sensitivity

- Female sex hormone levels influence nociception, but effects are not well understood
- Sex hormones may impact efficacy of analgesic drugs[8]
- The female rat estrous cycle - four stages characterized by fluctuations in hormone levels





OBJECTIVES

» To determine the effects of a KD on tactile sensitivity and pain sensitivity in female rats

» To determine whether current estrous cycle phase impacts the effects of a KD on tactile sensitivity and pain sensitivity

METHODS

Subjects

- Adult female rats (4 Sprague-Dawley, 4 Long-Evans)
- Pair housed in 12hr light/dark cycle, *ad libitum* access to food and water

Diet

- All animals maintained on a standard control diet (LabDiet 5001) through first round of testing
- Switched to strict 6.6:1 KD (BioServ F3666) and maintained for 3 weeks
- KD maintained through second round of testing

Tactile Sensitivity Testing

- Threshold to hindpaw withdrawal from pressure-sensitive electronic von Frey probe (Life Sciences Inc. Model 2390 Series)

Pain Sensitivity Testing

- Latency to hindpaw withdrawal from 50°C hot plate
- Withdrawal defined as stationary lifting or licking of either hindpaw

Estrous Staging

- Samples obtained by vaginal lavage after testing
- Stained with Hematoxylin and Schorr stains
- Estrous stage determined based on ratio of cell types and colors
- Metestrus and diestrus data combined due to similar hormone levels

RESULTS

TACTILE SENSITIVITY

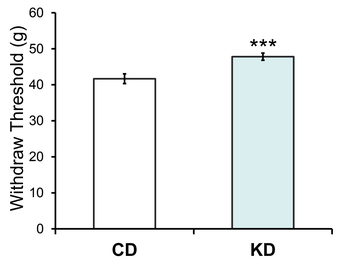


Figure 1. Tactile sensitivity is decreased in adult female rats fed a ketogenic diet

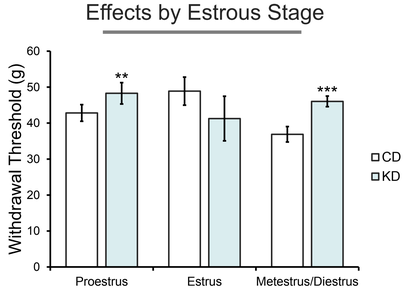


Figure 2. KD administration decreases tactile sensitivity during proestrus and metestrus/diestrus.

PAIN SENSITIVITY

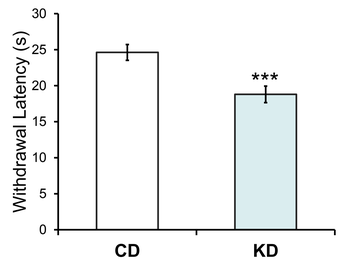


Figure 3. Thermal pain sensitivity is increased in adult female rats fed a ketogenic diet

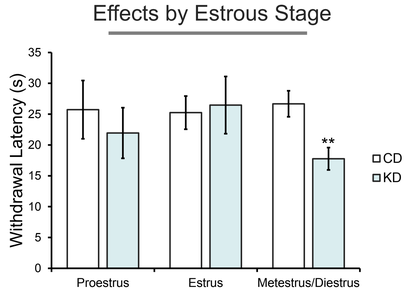


Figure 4. KD administration decreases thermal pain sensitivity during proestrus and metestrus/diestrus.

All data are presented as mean ± SEM.
**p<0.01, ***p<0.001 vs. CD. (*n*=8 per treatment group)

CONCLUSIONS

- KD treatment had opposite effects on tactile sensitivity and pain sensitivity
- May have differing impacts on nociceptive vs. non-nociceptive signaling pathways
- Increased pain sensitivity during KD treatment was unexpected

Possible Pronociceptive Mechanisms

- Increased adenosine A_{2A} receptor activation increases neuronal excitability
- Intradermal administration of adenosine increases pain sensitivity through A_{2A} receptors in male rats[9]

Female Sex Hormones

- KD effects were dependent on estrous cycle stage
- Impact of sex hormones on adenosine activity may influence KD effects
- Estradiol increases expression of adenosine deaminase[10]
- Ovariectomy of female rats decreases adenosine A_1 and A_{2A} receptor expression[11]

FUTURE DIRECTIONS

- Continuation of the study with a larger sample sizes may further elucidate findings
- Further investigation of KD treatment in females needed to confirm sex-based differences in nociceptive effects
- Use of ovariectomized females to may allow more precise determination of sex hormone effects

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