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 A₁ receptors
- Enhanced GABAergic neuronal inhibition

Potential Antinociceptive Effects
- Anticonvulsant medication used to treat neuropathic pain
- Adenosine A₁ receptor activation decreases tactile sensitivity and pain sensitivity in mice
- GABA signaling decreases nociception

Potential as a Treatment for Chronic Pain
- Current chronic pain treatments offer poor long-term efficacy
- KD administration decreases tactile hypersensitivity and thermal pain sensitivity in male rats

Sex Hormones and Pain Sensitivity
- Female sex hormone levels influence nociception, but effects are not well understood
- Sex hormones may impact efficacy of analgesics
- 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

Diets
- 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

RESULTS

TACTILE SENSITIVITY

PAIN SENSITIVITY

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

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

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

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

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 A₁ receptor activation increases neuronal excitability
- Intradermal administration of adenosine increases pain sensitivity through A₁ receptors in male rats

Female Sex Hormones
- KD effects were dependent on estrous cycle phase
- Impact of sex hormones on adenosine activity may influence KD effects
- Estradiol increases expression of adenosine deaminase
- Ovariectomy of female rats decreases adenosine A₁ and A₂A receptor expression

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 ovariocytomized females to may allow more precise determination of sex hormone effects

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REFERENCES