The Effects of Eating a Traditional High Fat or a Ketogenic Diet on Sensitivity of Female Rats to Morphine-Induced Antinociception, Tolerance and Withdrawal

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Opioid drugs like morphine are used for pain relief but also have high abuse potential. Further, individuals diagnosed with obesity are at a greater risk for opioid overdose. While overconsumption of a high fat diet can lead to obesity, it is not known if diet impacts sensitivity of individuals to morphine. To explore this possibility, the effects of morphine under acute and chronic conditions, as well as non-precipitated withdrawal were assessed in 24 female Sprague Dawley rats (n=8/group) eating a standard laboratory chow (17% kcal from fat), a traditional high fat/high carbohydrate chow (60% kcal from fat), or a ketogenic (high fat/low carbohydrate) chow (90.5% kcal from fat). Morphine-induced antinociception was measured using the warm water tail withdrawal procedure. To explore the adverse effects of morphine, body weight, food consumption, fecal output, respiration, and body temperature were recorded periodically throughout the study. To study the effects of chronic morphine exposure, morphine was administered intraperitoneally (IP) twice daily for 19 days (3.2-56 mg/kg) increasing in 1 log doses every 3 days. Finally, after chronic morphine administration, observational signs of non-precipitated withdrawal and changes in body weight were measured following morphine discontinuation. It was hypothesized that rats eating high fat chow would be more sensitive to the acute effects of morphine (0.32-17.8 mg/kg IP) than rats eating other diets. It was further hypothesized that rats eating high fat chow would also be more sensitive to the development of tolerance to the antinociceptive effects (3.2-56 mg/kg IP) and withdrawal symptoms following chronic morphine administration, as compared to rats eating a ketogenic or standard chow. Morphine-induced antinociception was comparable among rats eating different diets when tested under acute conditions, and there were also no group differences in morphine-induced changes to respiration or body temperature. Fecal output was consistently greater for rats eating standard chow as compared to rats eating high fat or ketogenic chow following saline injections, as well as following acute or chronic morphine administration. After chronic morphine administration, all rats developed tolerance to morphine–induced antinociception. Specifically, the antinociception dose-response curves shifted rightward 8.2-fold for rats eating standard and high fat chow, and 4.4-fold for rats eating ketogenic chow. That is, tolerance was reduced (or less developed) for rats eating ketogenic chow as compared to other groups. Finally, morphine discontinuation resulted in observable withdrawal signs among all rats; however, there were no group differences except regarding withdrawal-related weight loss. Specifically, rats eating ketogenic chow experienced less withdrawal-related weight loss as compared to the other groups. These results suggest that tolerance to the pain relieving effects of opioid medications, as well as withdrawal symptoms, might be blunted by consuming a ketogenic diet. Future studies will examine the effects of dietary manipulation on drug sensitivity in the context of inflammatory pain.

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