Intergenerational influence of paternal obesity on metabolic and reproductive health of the offspring: Male-preferential impact and potential involvement of Kiss1-mediated pathways

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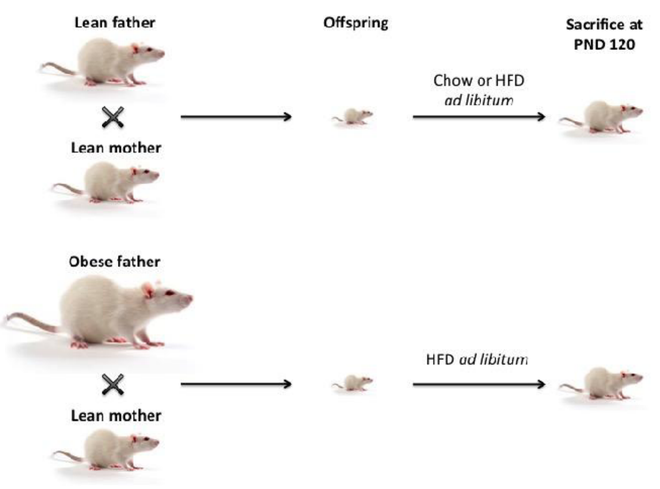
INTRODUCTION & OBJECTIVES

Obesity and its related comorbidities are reaching epidemic proportions (1). Maternal obesity is known to predispose the offspring to obesity and related metabolic disorders independently of genetic inheritance (2,3). This intergenerational transmission of metabolic derangements has also been suggested for paternal obesity during the pre-conception stage, as it appears to have a negative impact on the metabolic and reproductive health of the offspring (4,5), likely via epigenetic changes in spermatozoa (6). However, whether paternal obesity sensitizes the offspring to the metabolic and reproductive disturbances induced by high fat diet (HFD) remains poorly defined. We report herein the metabolic and reproductive impact of HFD in the offspring from obese fathers, paying special attention to identify potential sex differences and alterations on kisspeptin actions.

METHODS

Lean and extremely obese male rats (obtained by inducing early postnatal overnutrition coupled to HFD after weaning) were mated with lean and virgin female rats. Male and female offspring from lean and obese fathers were fed HFD from weaning onwards. At postnatal day 120 (PND120), the offspring were euthanized and several metabolic and reproductive parameters analyzed.

Experimental design



RESULTS

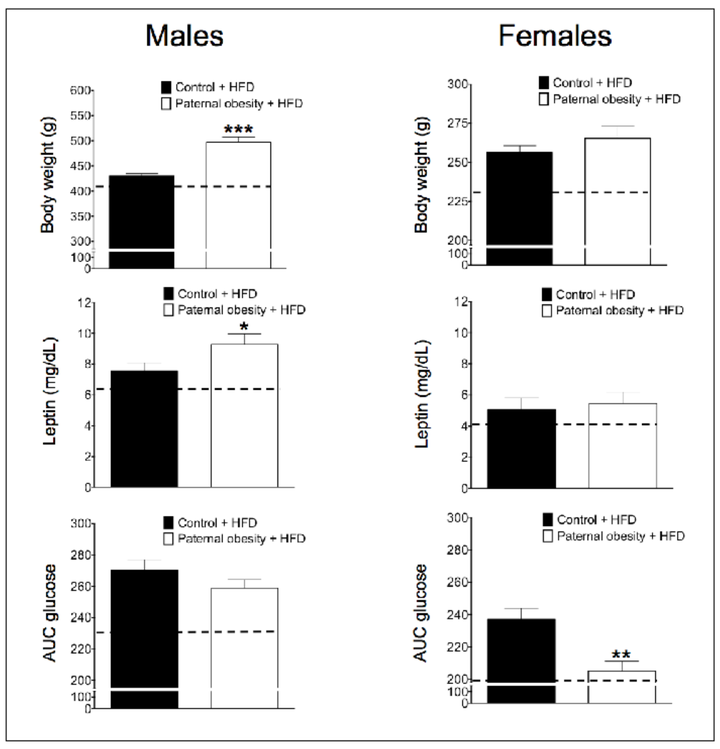


Figure 1. Metabolic impact of HFD in offspring from lean and obese fathers. Dotted lines represent values for chow-fed control mice from lean fathers. Data are presented as mean ± SEM. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

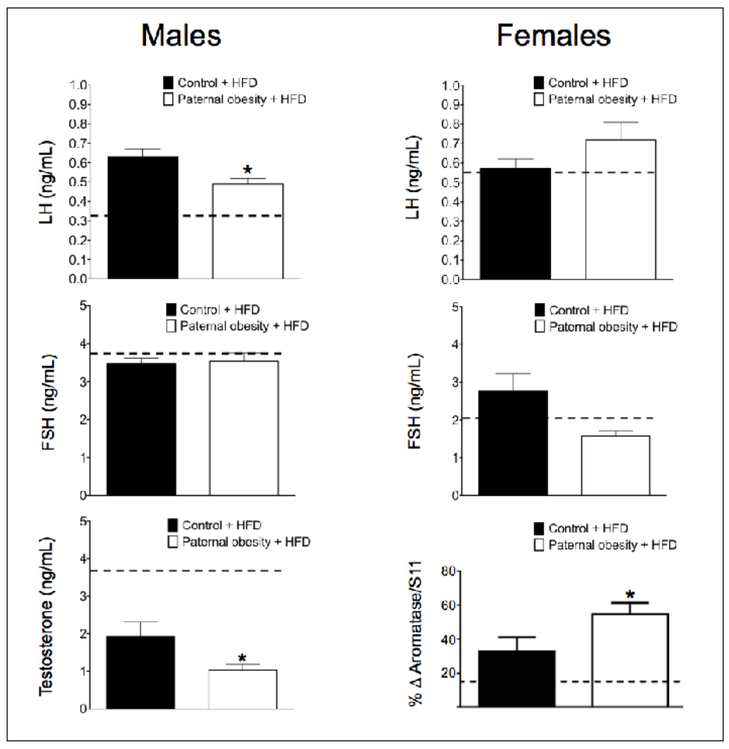


Figure 2. Reproductive impact of HFD in offspring from lean and obese fathers. Note that estradiol levels in females were not determined because of the methodological difficulties to accurately measure this hormone by conventional immunoassays. Instead, aromatase expression levels in the ovary were analyzed as a surrogate marker of circulating estradiol levels. Dotted lines represent values for chow-fed control mice from lean fathers. Data are presented as mean ± SEM. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

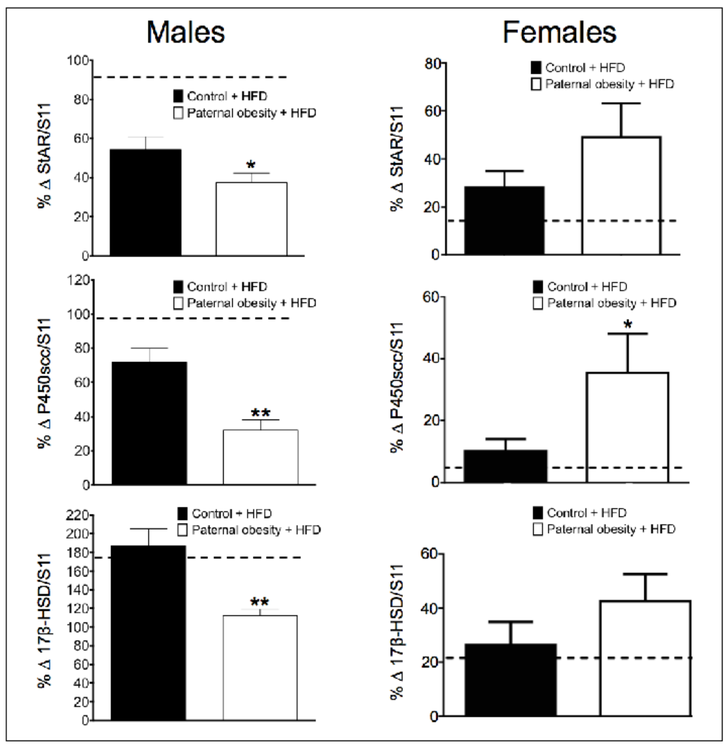


Figure 3. Impact of HFD on key enzymes involved in gonadal steroidogenesis in offspring from lean and obese fathers. Dotted lines represent values for chow-fed control mice from lean fathers. Data are presented as mean ± SEM. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

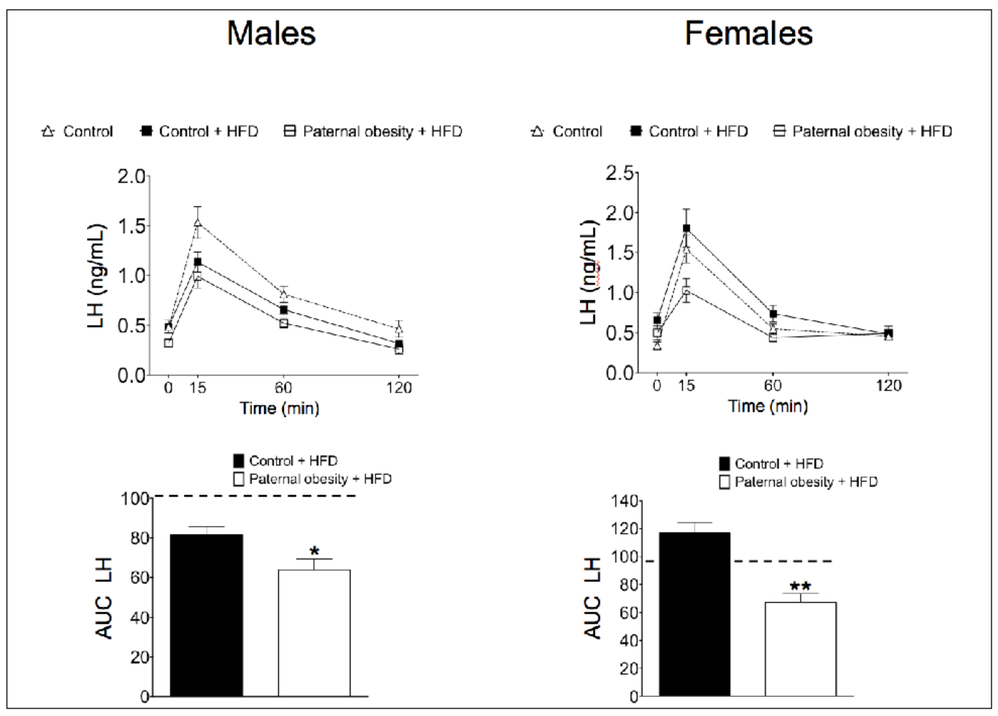


Figure 4. Impact of HFD on LH responses to central kisspeptin-10 administration in offspring from lean and obese fathers. Dotted lines represent values for chow-fed control mice from lean fathers. Data are presented as mean ± SEM. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

The increase in body weight and leptin levels, but not glucose intolerance, induced by HFD was significantly higher in the male offspring from obese fathers (**Figure 1**). In contrast, no differences were detected in the female offspring from both paternal groups (**Figure 1**); actually, glucose intolerance was lower in HFD-fed females from obese fathers. Paternal obesity caused a decrease in LH levels and exacerbated the drop in testosterone caused by HFD (**Figure 2**), which was associated to reduced testicular expression of key enzymes of testosterone biosynthesis (**Figure 3**). In addition, LH responses to central kisspeptin-10 administration were suppressed in HFD-fed males from obese fathers (**Figure 4**). Conversely, paternal obesity did not significantly alter gonadotropin levels in HFD females (**Figure 2**); but increased aromatase mRNA levels in the ovary, which may be used as a surrogate marker of circulating estradiol levels (**Figure 2**). Supporting a potential increase in estradiol levels, paternal obesity was also found to increase ovarian P450scc mRNA levels (**Figure 3**) and tended to elevate expression levels of other steroidogenic enzymes in HFD females (**Figure 3**). However, LH responses to kisspeptin-10 were dramatically reduced in HFD-fed females from obese fathers (**Figure 4**).

CONCLUSIONS

Our findings suggest that HFD-induced metabolic and reproductive disturbances are exacerbated by paternal obesity, mainly in males, while kisspeptin actions are affected in both sexes.

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