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Body fat affects mouse reproduction, ovarian hormone release, and response to follicular stimulating hormone

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ABSTRACT

We investigated the effects of body fat content on mouse fecundity, ovarian hormone release, and their response to follicle stimulation hormone (FSH). 4 types of females were produced: lean (group 1), normal (group 2), slightly fat (group 3), and significantly fat (group 4). The body weights, fat content, fertility rate, embryo number produced, retarded and degenerated embryo percentage, the release of progesterone (P4), testosterone (T), and insulin-like growth factor I (IGF-I) by isolated ovaries cultured with and without FSH (1.0 IU/mL medium) were evaluated. A gradual increase in body weight and fat contents from groups 1 to 4 was observed. Group 2 had higher fertility rate than those from the other groups. Groups 2 and 3 had fewer retarded and degenerated embryos that those from groups 1 and 4. Embryo production rate was not different among the groups. P4 and T secretion was higher from group 4 than in those from groups 1–3; secretion of IGF-I of group 3 was less than that of groups 1, 2, and 4. FSH promoted ovarian T output in all groups and stimulated ovarian P4 release in groups 1, 3, and 4, but not in group 2. FSH did not affect IGF-I release in any group. Therefore, both malnutrition and overfeeding can affect body weight and fat content in female mice, reducing embryo quality or developmental capacity, but not fertility and embryo production. Excess weight or fat can have stimulatory effects on ovarian P4 and T, but inhibitory effects on ovarian IGF-I release. Both leanness and excess weight or fat can induce the stimulatory action of FSH on ovarian P4.

1. Background

Understanding the characteristics and mechanisms of the metabolic control of reproduction is important from theoretical, practical, and medical viewpoints, especially considering the current epidemic of human and pet obesity. Negative energy balance has been found to suppress reproduction and fecundity in pigs [1,2], cows [3–7], and mice [8,9]; however, it is not as acute as in rabbits [10] and in women [11]. Moreover, in rabbits, food restriction could promote ovarian functions and fecundity [12,13]. Conversely, increased fat content has been shown to induce infertility and ovarian and embryonal malformation in women [11,14], cows [4,16,17], and mice [8,9,15,18–24]. However, some studies found no negative effect of high-fat diet-induced obesity on the fecundity of cows [16,25,26], sheep [26], or women [27–29]. Moreover, administration of omega-6 fatty acids promoted bovine embryo yield in vivo and in vitro [4,30,31]. Therefore, the available evidence concerning the influence of either positive or negative energy balance on reproduction remains inconclusive.

The endocrine mechanisms mediating the influence of the metabolic state on reproduction are not yet known. Ovarian functions are under the control of gonadotropins (follicle-stimulating hormone, FSH; luteinizing hormone, LH), ovarian peptides (e.g., insulin-like growth factor, IGF-I), and steroid hormones [4,32]. In ruminants, a negative energy balance might restrict the release of gonadotropin-releasing hormone (GnRH) and the downstream gonadotropins, reduce the response of the ovarian tissue to gonadotropins, and restrict the development of ovarian follicles [4,33,34]. Conversely, the development of adipose tissue in ruminants and humans can promote the production of

Abbreviations: BSA, bovine serum albumin; eCG, pregnant mare's serum gonadotropin; FSH, follicle stimulation hormone; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; IGF-I, insulin-like growth factor I; LH, luteinizing hormone; P4, progesterone; RIA, radioimmunoassay; T, testosterone

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adipokine leptin, insulin/IGF-I [4,35,36], and ovarian steroid hormones [37,38], which are the known regulators of ovarian functions [32]. In mice, adipokine leptin [39] and adiponectin [40] can promote hypothalamic GnRH neurone development, ovarian LH receptor and steroidogenic enzyme expression, pituitary FSH and ovarian progesterone and testosterone release, puberty, and fecundity. These findings suggest multiple mechanisms of leptin and adiponectin action on reproductive processes, including up-regulation of hypothalamic GnRH, pituitary gonadotropins, and ovarian gonadotropin receptors and steroidogenesis.

Mice could be a good model to understand the endocrine mechanisms of metabolism influence on reproduction. Although no influence of negative energy balance on mice fecundity has yet been reported, lean mice had lower plasma leptin and insulin levels and exhibited a higher corticosterone response to stress compared to those with higher fat content, although stress or high corticosterone level reduced embryo quality [9]. Fat mice showed reduced fecundity and embryo quality [18–24], increased ovarian and embryonal cell apoptosis [22], increased embryonic IGF-I receptor, plasma leptin, and IGF-I expression levels, and lowered the correlations between plasma leptin and body weight and plasma IGF-I and IGF-I receptors, suggesting the resistance of target cells to feedback action of leptin and IGF-I [18,41]. Furthermore, fat mice were characterized by the overexpression of somatostatin, apolipoprotein A4, calcitonin and its receptor, and corticotropin-releasing hormone receptor 1 [42], the hormones which, together with leptin and IGF-I, are considered as markers and regulators of adiposity [1–5,11,32,35,42]. Taken together, the available evidence indicates the influence of the metabolic state/fat content on IGF-I, leptin, gonadotropins, and steroid hormones, which in turn control reproduction. This might indicate that these hormones mediate the effect of the metabolic state/fat on ovarian function and embryogenesis. However, the endocrine mechanisms of the influence of either negative or positive energy balances on mouse reproduction have not been sufficiently studied, and the roles of gonadotropins, ovarian IGF-I, and steroid hormones in these mechanisms are not yet known. The similarity in genetic distribution of both body condition and reproductive types, the effect of both malnutrition and overfeeding on mice and humans [12–14,18–24,34–37,42], and the influence of endocrine regulators of reproduction [32–35] and the mediators of metabolic state on reproduction in mice and human [18,32,34–40] suggest that mice might be suitable and convenient model for such studies and could contribute to contemporarily solving the problem of human obesity.

This study aimed to understand the endocrine mechanisms (the role of progestogens, androgens, and IGF-I and their response to FSH) in mediating the influence of the metabolic state or fat mass on murine ovarian functions. We attempted to (1) determine the influence of fat on mouse fertility rate, embryo production, and embryo quality; (2) evaluate the release of progesterone (P4), testosterone (T), and IGF-I by ovaries of mice with different fat mass; and (3) compare the response of the ovaries to FSH. In this study, we used the previously validated two-generation model [8,9,22,23]. This method results in the production of offspring with a heterogeneous predisposition for and manifestation of high fat mass at the time of sexual adulthood, resembling the human population heterogeneity in fat storage.

2. Materials and methods

2.1. Animals and experimental design

All animal experiments were reviewed and approved by the Ethics Committee for Animal Experimentation at the Institute of Animal Physiology and approved by the State Veterinary and Food Administration of the Slovak Republic (Ro 2296/13-221). They were performed in accordance with Slovakian legislation based on EC Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes.

All experiments were performed on female mice of the outbred ICR strain (Velaz, Prague, Czech Republic) divided into 4 groups according to their body condition or fat content:

(1) Group 1: lean animals derived from dams fed a standard diet (body fat content, < 7% of total mass)
(2) Group 2: normal animals derived from dams fed a standard diet (body fat content, 7–8% of total mass)
(3) Group 3: slightly fat animals derived from dams fed a high-energy diet (body fat content, 8–11% of total mass)
(4) Group 4: significantly fat animals derived from dams fed a high-energy diet (body fat content, > 11% of total mass).

These animals were obtained by using the two-generation dietary model. Adult female mice (35 days old) of the parental generation were subjected to hormonal synchronization and stimulation with pregnant mare's serum gonadotropin (eCG 5 IU ip; Folligon, Intervet International, Boxmeer, the Netherlands); after 47 h, human chorionic gonadotropin (hCG; 4 IU ip; Pregnyl, Organon, Oss, Holland) was administered, and the females were mated with males of the same strain overnight. Fertilized mice were individually housed in Plexiglass cages under standard conditions (temperature, 22 ± 2 °C; humidity, 55 ± 5%; 12:12 h light-dark cycle with lights switched on at 5:00, with free access to food and water). During the gestation (21 days) and lactation (from birth to weaning, 21 days) periods, donor dams from groups 1 and 2 were fed a standard pellet diet (M1, Ricmanice, Czech Republic; 13.4 kJ/g, with 26.3% energy as protein, 9.5% as fat, and 64.2% as carbohydrate; the remaining 3.8% was as cellulose and hemicellulose). Donor dams from groups 3 and 4 were fed a standard M1 diet with the addition of the high-energy product Ensure Plus (liquid diet containing 6.3 kJ/mL, with 15% of the metabolizable energy content as protein, 28% as fat, and 57% as carbohydrate) *ad libitum*. The litter size was adjusted on the eight day after birth to 10 or fewer pups per nest. The impact of actual nutrition on the reproductive process was minimized by feeding all F1 mice the standard diet after weaning.

When they reached the age of 35 days, the females were individually weighed and scanned using a Whole Body Composition Analyser EchoMRI (Echo Medical System, Houston, Texas, USA). This facility creates contrast between soft tissues by taking advantage of the differences in relaxation times of hydrogen proton spins in different environments and measures whole body fat, lean, free water, and total water masses in live animals. Fat is the mass of all the fat molecules in the body expressed as equivalent weight of canola oil. Lean is a muscle tissue mass equivalent of all the body parts containing water, excluding fat, bone minerals, and such substances that do not contribute to the NMR signal, such as hair, and claws. Values of body weight, total fat content (the mass of all fat molecules in the body), and total lean content (muscle tissue mass excluding fat and bone minerals) are expressed in grams (g). Relative fat contents are expressed as the percentages of body mass (calculated as body fat (g)/body weight (g) × 100). During this analysis, animals were allocated into 4 groups according to the percentage of their body fat, as listed above. Lean animals from group 1 had a low body fat content (< 7%); animals from group 2 manifested a normal physiological amount of body fat (7–8%); group 3 mice had slightly elevated body fat (8–11%); and dams from group 4 had highly increased body fat (> 11%).

2.2. Embryo recovery

Adult females of the F1 generation were used in the reproductive study. Preimplantation embryos were recovered from 5 to 6-week-old spontaneously ovulating female mice that had been mated by males during 1 or more nights. Mating was confirmed by the identification of a vaginal plug every morning at 7:30, and this point was designated day 1 of pregnancy. On day 4 post-mating (98–100 h post plug identification), dams from all groups were killed by cervical dislocation or

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