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Technical note

Maternal obesity alters the apelinergic system at the feto-maternal interface

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ABSTRACT

Apelin and its receptor APJ have been implicated in pathologies including cardiovascular disease, diabetes and obesity. Little is known about the function of the apelinergic system during gestation. We evaluated in mice this system at the feto-maternal interface in insulin-resistant obese female (HF) mice. Maternal apelinemia was decreased at term and fetal apelinemia was sixfold higher than maternal level. Ex-vivo, the placenta releases apelin at E12.5 and E18.5. In HF pregnant mice at term, apelinemia as well as placental apelin and APJ mRNA levels were increased whereas placental release of apelin was drastically reduced compared to controls.

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1. Introduction

Apelin is a regulatory peptide, identified as an endogenous ligand of the apelin receptor named APJ [1]. Apelin gene encodes a 77-amino-acid preproprotein that generates during post-translational processing several molecular isoforms such as apelin-36, apelin-17 and apelin-13 [2,3]. Apelin is an adipokine, also expressed across a wide range of tissues with its receptor APJ [4,5]. The apelinergic system is involved in numerous physiological processes such as vasoconstriction and dilatation, strengthening of heart muscle contractility, angiogenesis, and regulation of energy metabolism and fluid homeostasis [3,6]. Recently, apelin has been extensively described as a beneficial factor regarding to glucose metabolism and cardiovascular functions [7,8]. Little is known about the biology of the apelinergic system during pregnancy. APJ deficiency in mice causes early embryonic defects and leads to embryonic lethality due to growth retardation and cardiac malformations [9]. In humans, conflicting findings have been reported for this system under preeclampsia and gestational diabetes conditions [10,11]. To gain further insight into apelin/APJ physiology during gestation and its putative modulation by maternal obesity and/or diabetes, we investigated in normal mice and in insulin-resistant obese female mice fed with a high-fat diet (HF): 1/ the kinetics of apelin plasma levels in mother/fetus pairs during gestation and at term, 2/ the ex-vivo placental apelin release, 3/ the gene expression levels of apelin and APJ in the placenta at term.

2. Methods

2.1. Animals

5-week-old female C57BL/6 mice (Janvier, France) were randomized in two groups: a control (C) group (n = 30) fed with a standard diet (SAFE A04, containing 7% fat, 72% carbohydrate, 19%

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protein) and a HF group (n = 30) fed with a high-fat diet (Special Diets Service, containing 44% fat, 35% carbohydrate, 20% protein) during 11 weeks. Mice were weighed weekly and experiments were approved by the animal ethics committee from the University of Lille.

2.2. Oral glucose tolerance test and tissues collections during gestation

After 10 weeks, an oral glucose tolerance test (OGTT) was performed in C and HF mice after 6 h of fasting. Mice received an oral glucose load (2 g/kg) and blood glucose level was determined using a glucometer (Roche, France) after 0, 15, 30, 60, 90 and 120 min. Plasma samples were used for insulinemia measurement and insulin resistance was calculated using the HOMA-IR index. Then, mice were mated and they were weighed along the gestation. Ten mice of each group were sacrificed by decapitation at E6.5, E12.5 and E18.5 and trunk blood samples were collected. At E12.5 and E18.5, fetuses and placentas were collected after cesarean section and weighed. At E18.5, trunk blood samples of fetuses were collected and some placentas were frozen and stored at −80 °C.

2.3. Placental apelin release

After cesarean section, E12.5 and E18.5 placentas (n = 10/group/stage) were collected, cut in two pieces, and rinsed in saline and incubated for 24 h in dish plates containing 2 ml of DMEM (Gibco). Dish plates were placed at 37 °C with 95% O_2/5% CO_2 and 95%

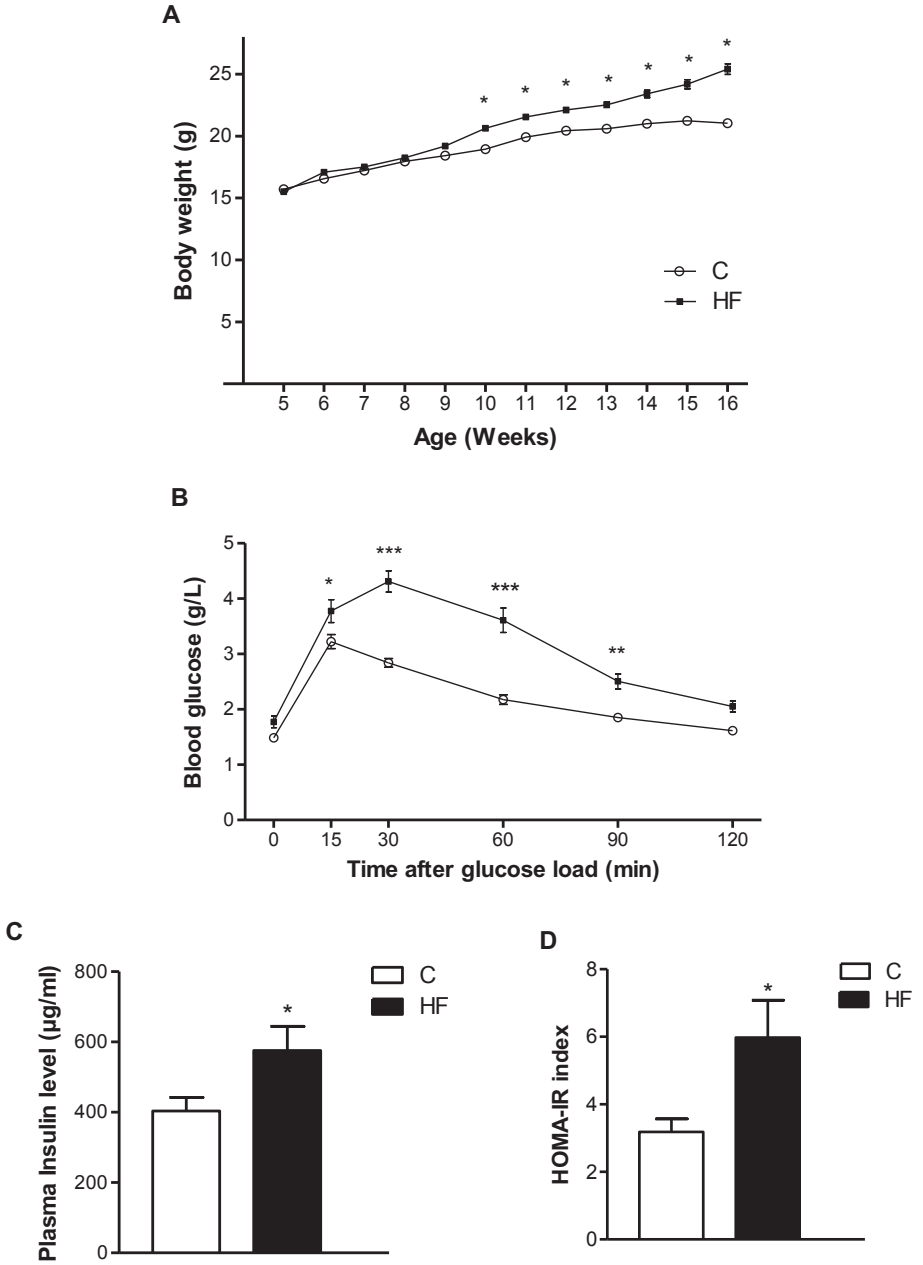

Fig. 1. Body weight curves of female mice from the age of 5 weeks–16 (A). Female mice were fed with a control (C) or a high-fat (HF) diet beginning at the age of 5 weeks (n = 30 mice/group). Oral glucose tolerance test (OGTT) in 15-week-old mice after 10 weeks of feeding with C or HF diet (B). Plasma insulin concentrations (C) and calculated HOMA-IR index (D) in 15-week-old C and HF female mice after 6 h of fasting. Values are means ± S.E.M. (n = 15 mice/group in Fig. 1B–D). *, P < 0.05; **, P < 0.01; ***, P < 0.001 HF vs C group.

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