GLP-1 REGULATES THE REPRODUCTIVE FUNCTION AND SYNCHRONIZES THE ONSET OF THE PUBERTY IN FEMALE RATS

Outeiriño Iglesias V, Romani Pérez M, Fandiño Gómez J, González Matías LC, Mallo Ferrer F and Vigo Gago EM.

Group LabEndo. Biomedical Research Center (CINBIO). Institute for Biomedical Research of Vigo (IBIV). Biocaps Project (EC).

University of Vigo. Vigo - SPAIN

INTRODUCTION

GLP-1 is an intestinal peptide with anorexigenic and insulinoinsulative effects. Exendin-4 (Ex4) is a GLP-1 agonist with longer half-life than GLP-1 used in the treatment of DM2. Previous studies from our group revealed the presence of GLP-1R in the three main levels of the gonadotrophic axis (hypothalamus-pituitary-gonads). In addition, GLP-1 but not Ex4 increases the amplitude of the pre-ovulatory surge.

OBJECTIVES: To evaluate the effects of native GLP-1(7-36)-NH2 (GLP-1) and Ex4 in the function of the reproductive system in adulthood and onset of puberty in female rats.

METHODS

STUDIES IN ADULTHOOD: Adult female rats were ivc injected with a single dose of GLP-1/Ex4 (1 nmol) or vehicle (Ve) in the morning of proestrus. Blood samples were taken by jugular venipuncture at different stages of the subsequent estrous cycle: Proestrus (P), Estrous (E), Diestrous-1 (D1) and Diestrous-2 (D2) for hormonal determinations (LH, FSH, Estradiol, Progesterone). Ovaries were isolated for histological studies: the number of mature follicles were determined in slides from ovaries at afternoon of proestrus. Slides from ovaries at D1 were used to determine ovulation rate (No corpus luteum/frat).

Another group of females was housed with males for mating that confirmed by sperm-positive vaginal plug. The dams were sacrificed by decapitation after delivery, and number of undelivered but implanted fetuses and neonates born were counted and weighed.

STUDIES IN PREPUBESCENCE: Prepubertal rats were treated ivc every 12h with GLP-1 (1nmol) or Ex4 (0.5nmol) for 8 days (27-35 d). Individual monitoring of body weight, food intake and vaginal opening (AV as an early indicator of the onset of puberty) was performed. Serial blood samples for subsequent determination of the LH levels were collected. After treatment, the animals were sacrificed and their ovaries and uteri were weighed.

RESULTS

<table>
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<th>ADULTHOOD</th>
<th>PUBERTY</th>
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![Figure 1](image1.png) Effect of GLP-1 or Exendin-4 administration (ivc) in gonadotropin and gonadal steroid levels of adult female rats.

Control injection of 1nmol of GLP-1 induced a significant increase in serum LH levels vs. vehicle group, at 18 pm of proestrus. Afterwards, LH levels decreased reaching nadir values at D2. Conversely, Ex4 significantly decreased LH levels, inducing a partial blockade of the LH pre-ovulatory surge (Fig. 1A).

A single dose of GLP-1 produced a significant increase in serum FSH levels vs. vehicle group, at 18 pm of estrous, but a significant reduction at D1. Ex4 nearly doubled FSH levels vs. control group, at proestrus afternoon (Fig. 1B).

GLP-1 produced a significant increase in Progesterone secretion at estrus and D1 (coinciding with the corpus luteum development). Moreover, Ex4 also induced a significant increase in Progesterone serum levels vs. vehicle group at estrus (Fig. 1C).

Acute treatment with GLP-1 produced a significant decrease in serum 17β-Estradiol levels vs. control group, at estrus. Ex4 decreased serum 17β-Estradiol levels at D2 (Fig. 1D).

![Figure 2](image2.png) Effect of central administration of GLP-1 and Ex4 in estrus and number of fetuses.

Ex4 treatment increased the ovulation rate to control group, with values slightly lower than those observed in ovulatory estrous and estrous treated with vehicle.

![Figure 3](image3.png) Effect of exogenous administration (ivc) of GLP-1 or Ex4 on food intake and body weight of prepubertal female rats.

Prepuberal treatment of 1 nmol/12h GLP-1 (ivc) did not change body weight or daily food intake during the experimental period (control group) (Fig. 3A and B). On the contrary, administration of 6/1000 nmol/12h of Exendin (ivc) induced a significant decrease in body weight and daily food intake vs control group (Fig. 3C and D). Because the effect of Ex4 is not clear, a group of prepubertal female rats were allowed access to the cafeteria. No changes in body weight and food intake was observed (Fig. 3E and F).

![Figure 4](image4.png) Indices of pubertal maturation recorded in female rats chronically exposed to GLP-1 or Ex4.

All animals treated with GLP-1 reached vaginal opening at day 22 of portament development (average 22.07 ± 0.35, 193), while the control group showed a range between day 22.27 (mean age 0.25 ± 1.78 of portament 14). The pre-treatment group showed delayed pubertal onset (19 ± 0.13 ± 1.204) vs. control group. Ex4 treatment animal failed to enter the puberty showing no vaginal opening in any case (Fig. 4A). Vg data are expressed as a percentage of the total number of animals for each experimental group.

Prepuberal administration of GLP-1 increased LH levels (Fig. 4B), although not modifying the weight of uterine and ovarian features vs control (Fig. 4C and D). However, Ex4 treatment significantly decreased the levels of LH and weight of uterine and ovarian vs control group, acquiring a blockade in pubertal development. While the control group did not show any changes in LH levels, uterine and ovarian weights, vs control group.

CONCLUSIONS

GLP-1 increases the preovulatory surge of gonadotropins and ovulation rate in adulthood and synchronize the onset of puberty. These effects were not reproduced by Ex4.