EMOTIONAL BEHAVIOR IS MODULATED BY LIRAGUTIDE IN AN AGE AND GENDER MANNER IN RATS FROM FOOD RESTRICTION MOTHERS

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INTRODUCTION

Food restriction (FR) of mothers during the perinatal period, can generate disorders such as anxiety an hypersensitivity to stress in offspring and predisposes to the development of disturbances in emotional behaviour and psychological disorders in adulthood. In rodents, these alterations include changes in exploratory behaviour and increased behaviour associated to anxiety. Liraglutide, a GLP-1 receptor agonist, used as a treatment for Type 2 Diabetes Mellitus, is known to have several effects in the central nervous system, regulating the hypothalamic-pituitary-adrenal function, food intake and stress response, but also having important neuroprotective activities.

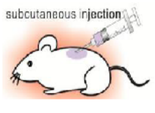
The **aim** of this study was to asses liraglutide given to pregnant rats may prevent the deleterious effects of FR in the anxiety-like behaviour in pups at 21 days and two months of age males.

MATERIAL AND METHODS

VAGINAL SMEAR Control of the estrous cycle and **mating (**25 ♀ and 10 ♂ *Sprague-Dawley* rats (12 weeks old) were used.

Separation of rats in individual cages and randomly determining groups (**CT/VEH, CT/LIRA, 50FR/VEH, 50FR/LIRA**).

Start of treatment with liraglutide (100µg/kg; s.c/12h) or vehicle (acetic acid (0.4%)+NaCl; s.c/12h)



FR 30%/*ad libitum for 21 days*

DAY 1 Vaginal plug

DAY 6

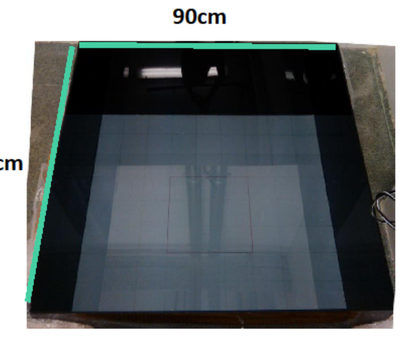
DAY 12 Frood restriction 50% in 50FR rats; *ad libitum* feeding in CT rats.

DAY 14

DAY 21 Birth

DAY 21 before weaning
Open field test to determine anxiety-like behavior in 40 ♂ and 39 ♀

TWO MONTHS
Open field test to determine anxiety-like behavior in 40 ♂



In this test we assessed the anxiety-like behavior using the open field test, evaluated the percentage of time the animal remains in the different areas of open field; 10, 20, 30cm, corner and center, classifying such behavior with varying degrees of anxiety.
It is done between 9 and 12am for 10 minutes. Animal performance was taped with a video camera for posterior analysis.

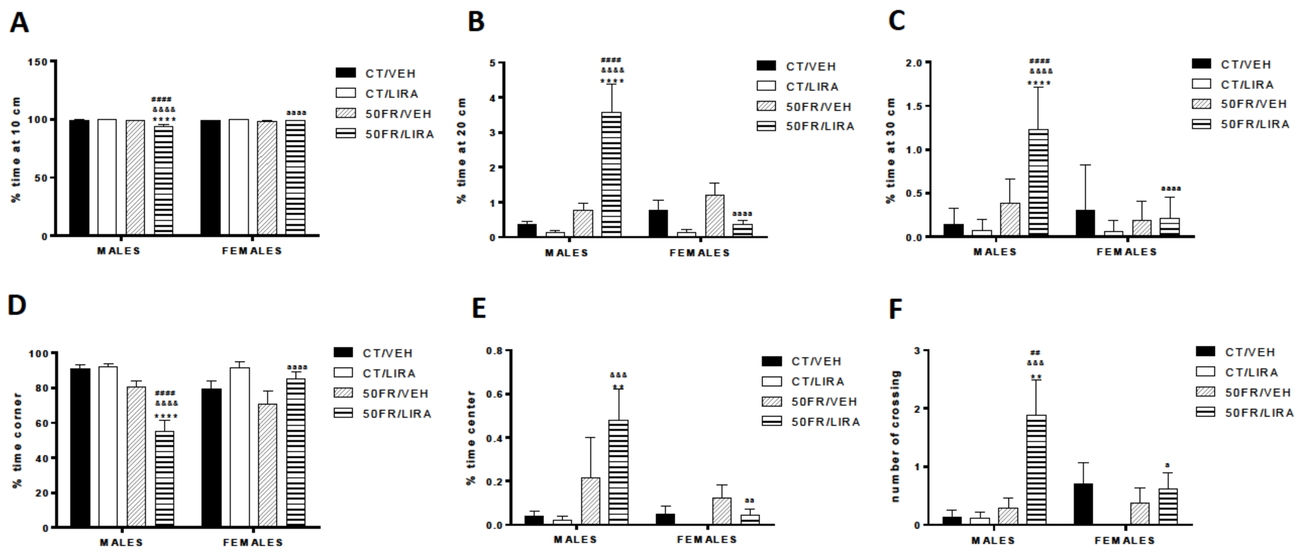
Statistical analysis was performed using the statistical program GraphPad Prism, test two-way ANOVA was used, considering as variables sex and treatment. The test of multiple comparisons was used to compare sex was the Sidak, and for comparing treatment was Tukey. Differences were considered significant when p≤0.05.

"*" Statistically different between CT / VEH and 50FR / LIRA; **"&"** Statistically different between CT / LIRA and 50FR / VEH; **"#"** Statistically different between 50FR / 50FR VEH; **"a"** statistically different between males and females 50FR / LIRA.

******,&&&&,####,aaaa : p<0.0001** **&&&: p<0.001** ****:,##: p<0.01** **a: p<0,5**

RESULTS

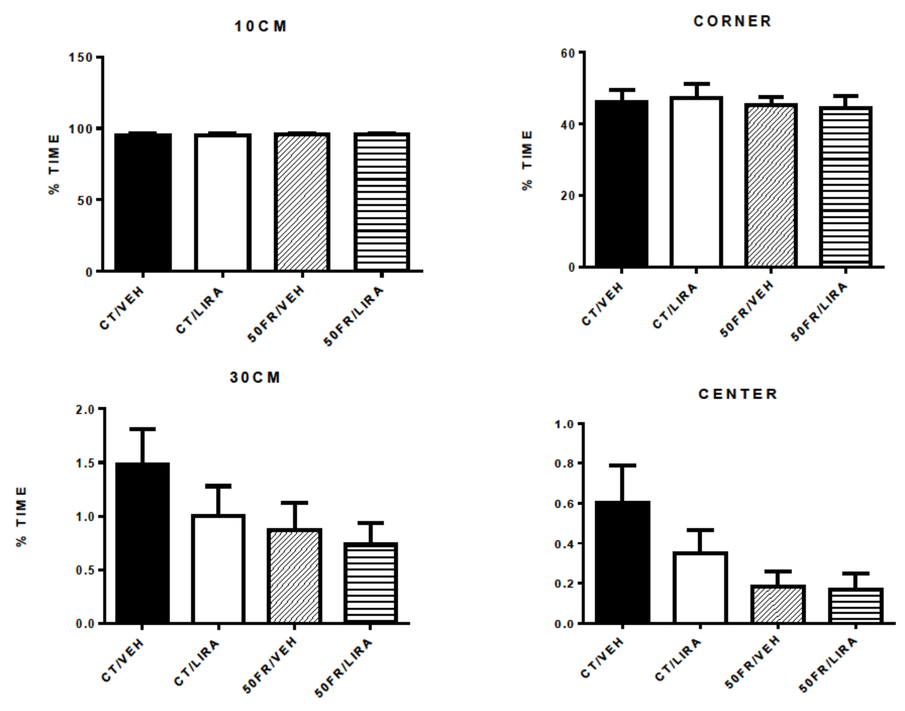
Study of the anxiety-like behavior in males and females in the corner, 10, 20, 30cm and in the center, at day 21.



There were no differences in the time spent in **10** (A), **20** (B), **30** (C) cm or **corner** (D), nor in anxiety-like behavior between vehicle treated males or females (50FR or CT). However treatment with liraglutide decreased significantly the time spent in 10 cm and corner, and increased the time spent in 20 or 30 cm only in 50FR males but not in females. Liraglutide has anxiolytic effects, increasing the percentage of time that 50FR-males spent in the **center** (E), and the **number of crosses** they made (F). In females no significant differences were observed.

When we compared results obtained in males and females no significant differences were observed in the number of crossings or the percentage of time that the offspring spent in the center in the control groups, but there were differences among the male and the female of FR group treated with liraglutide, since males spent more time in the center, and the number of crossings was higher.

Study of the anxiety-like behavior in males in 10, 30cm and in the center, at 2 months.



At two months of age, there are no differences in time spent in **10**, **corner**, **30** and **center,** irrespective to the treatment of the mothers.

Regardless of being treated or not with liraglutide, it was observed that caloric restriction during pregnancy increased the anxiety-like behaviour.

CONCLUSIONS

In conclusion besides FR did not induce behavioral alterations at 21 days or two months of age, liraglutide reduced the % of time in the center only in 50FR male pups, indicating an age-dependent effect of liraglutide under non-stressed conditions.