Maraviroc, a CCR5 Antagonist, Alters Gut Microbiota Composition in a Mouse Model of Obesity

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INTRODUCTION

-Changes in intestinal microbiota, through their effects on energy homeostasis and inflammation, could contribute to the development of several pathologies (1,2). Thus, preservation of gut microbiote composition arises as a promising tool to prevent the development of different disorders such as obesity.

-Maraviroc (MVC), a CCR5 antagonist approved for the treatment of HIV-infected patients, have showed neutral or even beneficial effects on liver and adipocyte metabolism (3,4) suggesting beneficial actions in overweight/obese HIV-infected patients. However, MVC impacts on gut microbiota have not been analyzed yet.

-The aim of this study was to investigate the effects of MVC on gut microbiota composition in a mouse model of obesity.

METHODS

A total of 32 male C57BL/6 mice were randomly assigned to one of the following groups: a) Control group (chow diet), b) MVC group (chow diet plus 300 mg/L MVC in the drinking water) c) High-fat diet group (HFD) or d) HFD+MVC group. Body weight and food intake was recorded 3 days per week. All mice were euthanized after 16 weeks of treatment and cecal contents were removed to study gut microbiota composition. We analyzed four orders from the most dominant phyla in gut by real time PCR.

Statistical differences and interactions were evaluated through a two-way ANOVA. When statistically significant differences resulted at the interaction level (DxMVC), Student's t-test was carried out to compare the effects of each treatment.

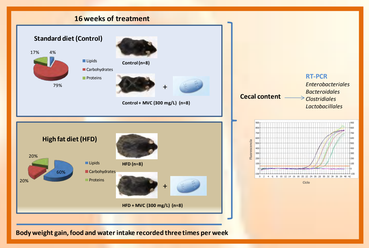


Figure 1: methodology followed in this study.

RESULTS

1.- BODY WEIGHT GAIN AND BIOCHEMICAL PARAMETERS

HFD induced a significant increase in final body weight and body weight gain ($p<0.001$). MVC showed a tendency to decrease this body weight gain despite the ingestion of the HFD ($p=0.06$). The same pattern was observed when glucose, insulin and HOMA index was analyzed. (Table 1).

Table 1: Effects of MVC on body weight gain, food intake, glucose, insulin and HOMA index in control and high-fat-fed mice

	Control	MVC	HFD	HFD+MVC	2x2 Diet	2x2 MVC	2x2 Diet x MVC
Initial Weight (g)	19.2 ± 0.2	19.1 ± 0.3	19.0 ± 0.3	18.1 ± 0.4	ns	ns	ns
Final Weight (g)	26.9 ± 0.3	28.0 ± 0.5	47.6 ±1.0***	43.1 ± 1.5***^{a}	-	-	P<0.01
Weight gain (g)	7.7 ± 0.2	8.8 ±0.3	28.6 ±0.8***	24.9 ± 1.6***^{b}	-	-	P<0.05
Food intake (cal/day)	20.2 ±0.1	21.4 ±0.01	34.9 ± 0.6	37.9 ± 1.7	P<0.001	P<0.05	ns
Glucose (mg/dL)	289.7 ± 12.6	323.3 ± 25.4	413.3 ± 26.1	382.5 ± 11.9^b	P<0.001	ns	ns
Insulin (ng/mL)	0.6 ± 0.04	0.8 ± 0.08*	4.5 ± 1.1	3.3 ± 0.4	P<0.001	ns	ns
HOMA index	9.8 ±0.9	17.5 ± 1.9*	124.8 ± 36.2	69.0 ±6.6	P<0.001	ns	ns

*p<0.05 and ***p<0.001 *vs*. control; ^{a}p<0.05 and ^{b}p=0.06 *vs*. HFD

2.- *ENTEROBACTEROIDALES*

Mice fed with a HFD showed a significant increase in the expression of *Enterobacteriales* in comparison with the controls ($p<0.001$). MVC treatment induced a significant decrease in the mRNA levels of this order in both control and HFD mice ($p<0.05$).

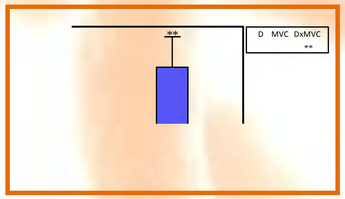
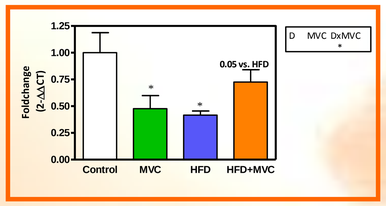
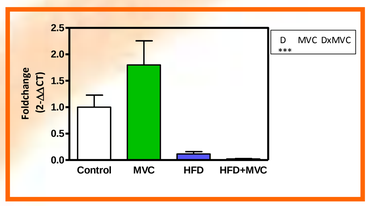


Figure 2: *p<0.05 and **p<0.01 *vs*. control; ^{a}p<0.05 *vs*. HFD

3.- *BACTEROIDALES* AND *CLOSTRIDIALES*

HFD induced a significant decrease in *Bacteroidales* and *Clostridiales* mRNA levels ($p<0.05$ and $p<0.001$ respectively). MVC decreased the expression of *Bacteroidales* in the group of animals fed with a control diet ($p<0.05$) while a tendency to increase the expression of this order was observed in HFD mice ($p=0.05$). No direct effects were observed on *Clostridiales* after MVC supplementation, although a slightly decrease was observed in HFD mice.

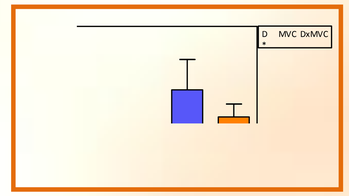




Figures 3 & 4: *p<0.05 and ***p<0.001 *vs*. control.

4.- *LACTOBACILLALES*

HFD significantly increased the mRNA levels of *Lactobacillales* ($p<0.05$) while no significant effects were observed after MVC supplementation, although a tendency to decrease the expression levels of this order was observed in HFD mice.



Figures 5: *p<0.05 *vs*. control

CONCLUSIONS

-MVC modified gut microbiota composition, being specially evident the effects observed on *Enterobacteroiales* and *Bacteroidales* orders.

-MVC actions seem to be dependent on diet composition and the metabolic status of animals.

-More studies are needed to further investigate if these changes on microbiota composition could have a significant clinical impact.

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