Chronic Oleoylethanolamide Treatment in Diet-Induced Obese Rats: Effect on Food Intake, Body Weight and Gut Microbiota

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Oleoylethanolamide (OEA) is an endogenous lipid generated in the intestine upon the ingestion of fat. As a drug, OEA was able to reduce food-intake and body-weight-gain (BWG) in both lean and obese rodents (Romano et al., 2015).

The excessive consumption of high-fat-diet (HFD) is responsible for the development of a diet-induced obese phenotype (DIO), characterized by a significant decrease in intestinal OEA levels (Igarashi et al., 2015) and changes in the composition of the gut bacterial community (Everard et al., 2014)

Based on these premises, in this study we investigated the anti-obesity effects of OEA in a rat model of DIO, not only focusing on the regulation of feeding behavior and BWG, but also on the composition of the gut-microbiota.

In our protocol rats were given free access to a HFD (60% calories from fat) for 11 weeks and were then split into three groups remaining on a HFD for two extra weeks: one free-feeding group (HFD-O) was treated daily with OEA (10 mg/kg intraperitoneally), one free-feeding group (HFD-V) was administered daily with vehicle, and a third group of pair-feeding rats (HFD-pair) daily administered with vehicle and with no free access to food that received the average amount of food consumed by OEA-treated rats. This third HFD group was included to monitor the indirect anti-obesity effects of OEA due to the reduced caloric intake. An extra control group of rats fed for 13 weeks with a low fat diet (10% calories from fat) and daily administered with vehicle (LFD-V) during the last two weeks was also included in the study to monitor the effects produced per se by the HFD.

Food intake and body weight were daily monitored throughout the study and, at the end of the 13 weeks, all rats were sacrificed and cecal content were collected for the microbiota analyses.

Our results demonstrate that, as expected, OEA treatment significantly reduced BWG in DIO rats and this effect was not strictly dependent from the inhibition of caloric intake since it was significantly higher than the decrease of BWG observed in pair-feeding rats. Moreover, the reduction of caloric intake after OEA treatment was not immediately observed in DIO rats, as expected, but it rather became significant at the end of the first week of treatment. A similar time point was observed for the reduction of body weight. These observation suggest that both the behavioural and metabolic effects of OEA can be evident in DIO rats with a long-time HFD exposure only after an adequate adaptation time. We hypothesize that this adaptation includes rearrangements of the gut microbiota that might be involved in the effects produced by OEA.

In accordance with our hypothesis, we found a decreased number of total bacteria and a lower diversity of gut bacteria in the samples collected from DIO rats, as compared to those harvested from LFD-exposed rats. Both observations are in accordance with previous reports. Two-weeks OEA treatment was able to affect the general composition of the gut microbiota, independently from its hypophagic action, as suggested by the Principal Coordinates analyses (PCoA). When we focused on the different phyla, class or lower taxonomic levels of the bacteria we could appreciate the expected changes induced by the HFD exposure with respect to the LFD exposure and we were able to detect an effect of OEA on many of these changes. For some of the becteria affected, no similar differences were detected in the pair-feeding group of rats, thus again suggesting that the changes of gut microbiota composition are likely induced by a direct effect of OEA, rather than being a mere consequence of the reduced caloric intake.

Overall, our study provides important new information on the therapeutic potential of OEA for the treatment of obesity.

Romano et al. (2015) Front Pharmacol, 6:137

Igarashi et al. (2015) Biochim Biophys Acta, 1851:1218-26

Everard et al. (2014) Nat Commun, 5:5648