Modulation of energy homeostasis by endogenous lipid mediators: Therapeutic potential of Palmitoylethanolamide (PEA) and the GRP119,1-BOC ligand in the regulation of "diabesity".

Abstract. Obesity and diabesity are complex metabolic disorders characterized by an excess of adipose tissue, energy imbalances, and metabolic dysfunction. This study evaluated the effects of palmitoylethanolamide (PEA), 1-Boc-piperidine, and their combination on female Wistar rats predisposed to obesity from a high-fat diet. Researchers identified animals predisposed to obesity by observing their initial weight gain and subsequently administering treatment for 21 days. Researchers examined body weight, caloric intake, various biochemical markers, and the cellular composition of adipose tissue during this period. The results show that both PEA and 1-Boc-piperidine were linked to less weight gain in rats that were given only the vehicle, as well as changes in food intake and some metabolic markers. These findings appear to corroborate previous statements regarding PEA. For instance, it has been associated with improved metabolic regulation, adipose tissue remodeling, and the restoration of leptin sensitivity in preclinical models.
The data suggests that PEA and 1-Boc-piperidine may influence body weight gain and specific metabolic parameters in this experimental model; however, these findings should be interpreted with caution due to the small sample size, short treatment duration, and lack of direct mechanistic studies.

Introduction.

The term "diabesity" describes the obesity pandemic and its related condition, type 2 diabetes. These two complicated diseases are biomedical problems that we face in the 21st century (Melini et al., 2024; Michaelidou et al., 2023). This pathological state focuses not only on caloric imbalance, but also on low-grade inflammation, mitochondrial dysfunction, and metabolic inflexibility in critical organs such as the liver and adipose tissue (Annunziata et al., 2022; Branković et al., 2024). Even with improvements in pharmacology, we still need to find pleiotropic medicines that can work on more than one biological target to bring metabolic balance back to normal without the adverse effects of synthetic pharmaceuticals (Di Stefano et al., 2025; Melini et al., 2024).

In this context, lipid mediators belonging to the N-acylethanolamine (NAES) family have demonstrated efficacy in regulating energy balance (Matias et al., 2007; Medoro et al., 2024). Within this family, it is essential to distinguish the functions of oleoylethanolamine (OEA) from its structural analog, palmitoylethanolamide (PEA). OEA has been widely recognized for its ability to reduce food intake and promote satiety by activating the PPAR-1 receptor and the G protein-coupled receptor GPR119, acting primarily as a peripheral anorexigenic signal. (Matias et al., 2007; Overton et al., 2006). Conversely, PEA exhibits a distinctive pleiotrophic profile that aids in appetite regulation. OEA levels in adipocytes remain constant during differentiation, but PEA levels experience significant downregulation throughout adipocyte maturation and in subcutaneous adipose tissue associated with obesity (Hoareau et al., 2009; Matias et al., 2007). This deficiency suggests that the loss of PEA is a major event that substantially contributes to the pro-inflammatory state and endocrine dysfunction of adipose tissue (Hoareau et al., 2009).

Recent research identifies PEA as a significant insulin sensitizer and an activator of the AMPK/PPAR-β axis (Annunziata et al., 2022; Raso et al., 2014). Activation of these pathways not only promotes fatty acid oxidation and reduces hepatic steatosis but also induces the reprogramming of white adipose tissue toward a thermogenic "beige" phenotype (browning), thereby increasing basal energy expenditure (Annunziata et al., 2022). A strategic component in this regulatory network is the GPR119 receptor, whose activation regulates insulin secretion and satiety. The use of specific ligands such as 1-BOC-piperidine-4-carboxaldehyde (1-BOC) allows for the exploration of modulation with PEA and could enhance the restoration of metabolic flexibility (Di Stefano et al., 2025; Overton et al., 2006).

Beyond its systemic effects, PEA exerts a comprehensive protective function in the gut-brain axis. It has been shown to counteract biosynthesis, restore beneficial bacteria such as *Tiricibacter sanguinis,*

and modulate tryptophan metabolism to promote colonic serotonin biosynthesis, which is crucial for regulating intestinal function and emotional stability (Lama et al., 2022; Pirozzi et al., 2023).
The above findings reinforce the hypothesis that PEA supplementation together with selective activation of GPR119 by 1-BOC constitutes a promising strategy to reverse dysfunctions associated with obesity states.

Methods

Animals

Thirty-two female Wistar rats weighing 90g –110g at the start of the experiments were used. All rats in this study were kept on a 12/12 h light/dark cycle (light starting at 7:00 am), at a constant temperature of 22°C, and at 50% humidity. Food and water were provided *ad libitum* in all the selected animals.

All experimental protocols were conducted with the approval of the Institutional Ethics Committee and in strict accordance with national and international guidelines for the use of laboratory animals in the United States and the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines (Bayne, 1996; McGrath, Drummond, McLachlan, Kilkenny, & Wainwright, 2010).

Compounds and Foods Used

1-Boc-piperidine (1-Boc-piperidine-4-carboxaldehyde) and methanol were obtained from Sigma Chemical Co. (St. Louis, MO, USA). 1-Boc-piperidine was dissolved in 10% methanol. It is important to note that, since the injection volume for treatments was 1 ml/kg, administered intraperitoneally, the total amount of methanol received by the rats was approximately 20 µg three times per week. Note: Although methanol is a vehicle that can raise some concerns due to its potential for harmful effects, toxic doses in rodents are 500 times higher (Moral, Çankayalı, Sergin, & Boyacılar, 2015; Yazgan et al., 2017) than the dose used in this study (e.g., LD50 in rats = 9.5 g/kg) (Roe, 1982).

Freshly prepared solutions were used in each experiment. The anesthetic used to euthanize animals at the end of the study was isoflurane (Sofloran®, Laboratorios PiSA S.A. de C.V., Guadalajara, Jalisco, Mexico). The standard diet was obtained from Agribrands Purina México, S.A. de C.V., Mexico City, Mexico. Regarding high-calorie foods, Oreo® cookies (NABISCO®, Mondelez México, S. de R. L. de C. V., Mexico City, Mexico) were purchased.

Cafeteria Diet-Induced Obesity Model

To induce obesity, the “cafeteria diet” model was used, in which the effect of 1-Boc-piperidine and palmitoylethanolamide (PEA, a non-selective GPR119 agonist) alone or in combination was evaluated on body mass gain, food preference, and metabolic damage.

This obesity model consists of continuously exposing rats to cafeteria food. For this purpose, 200g croquettes were prepared using a mixture of Maria-type cookies (300g), Hershey's chocolate syrup (200g), rat food pellet powder (300g), sausages (400g), and lard (200g). The food was prepared by grinding the solid ingredients separately (cookies), the sausages in a blender, and the pellets in a coffee grinder. All ingredients were then kneaded until a homogeneous dough was obtained, from which the croquettes were formed. For 8 weeks, the groups had ad libitum access to cafeteria food, standard food (pellets), and water. The calories consumed by each group were analyzed daily. The animals in all groups were weighed before the start of the experiment and every 7 days until its completion.

Selection Criteria for Susceptibility to Obesity

Thirty-two female Wistar rats, housed in groups of 16 animals per cage, were exposed to a standard diet, drinking water, and a cafeteria diet for 5 weeks. Body mass gain was recorded weekly for 5 weeks. In week 1, the mean body mass value of the 32 rats was calculated and used as the cutoff point to classify the animals as either resistant to obesity (when the increase during week 1 was less than the mean) or susceptible (when the value was greater than or equal to the mean). This resulted in 20 susceptible rats and 12 resistant rats.

Pharmacological Treatment

Twenty female Wistar rats susceptible to obesity from a cafeteria diet were randomly assigned to 4 groups (n = 5 each) that received one of the following treatments: (i) vehicle; (ii) PEA; (iii) 1-Boc-piperidine; and (iv) Mixture (i.e., PEA + 1-Boc-piperidine). All groups had ad libitum access to water, standard feed, and cafeteria diet. Treatments were administered intraperitoneally every 24 h for the 21 days of the experiment. Treatments were administered in a total volume of 200 µL, containing PEA (0.16 µmol), 1-Boc-piperidine (2 µmol), a vehicle with 5% DMSO and 1.3% methanol, and the Mixture, which was the combination of the PEA + 1-Boc-piperidine doses. Weekly weight and daily calorie intake data were collected to assess feed preference.

Biochemical Analysis

Biochemical analyses in the ‘cafeteria diet’ model were performed in order to compare the effect of 1-Boc-piperidine and PEA, alone or in combination, on metabolic damage or protection in animals by studying total glucose, insulin, cholesterol, and triglyceride levels. At the end of the experiments, the rats were sacrificed, blood was drawn directly from the left ventricle of the heart, and the sera were separated and aliquoted for biochemical analysis. The rats were sacrificed as previously described; the thorax was opened, and blood samples (3 ml) were taken from the heart, centrifuged at 1500 RPM for 15 minutes, and the sera separated. While glucose levels were measured immediately, the remaining serum aliquots were frozen at -80°C for later evaluation.

Statistical Analysis

The results section presents the analysis obtained from the corresponding ANOVA according to Hartley's test, expressing for each result: the degrees of freedom of the total sample size (n-1), the degrees of freedom of the residual sample size (n-1), and the F-value, which indicates the variation between groups and the probability of a difference between these variations. Data were statistically analyzed with a significance level of $P < 0.05$. All figures are presented as mean ± SEM. Graphs and statistical analysis were performed using GraphPad Prism, version 9.0.2. Differences in the percentage changes in body weight were analyzed using a two-way ANOVA. Cookie consumption (kcal/min) was analyzed using a two-way repeated measures ANOVA. The Holm-Sidak or Dunnett post hoc multiple comparison procedure was used for all experiments. The rationale of the experiment is expressed in the Figure 1.

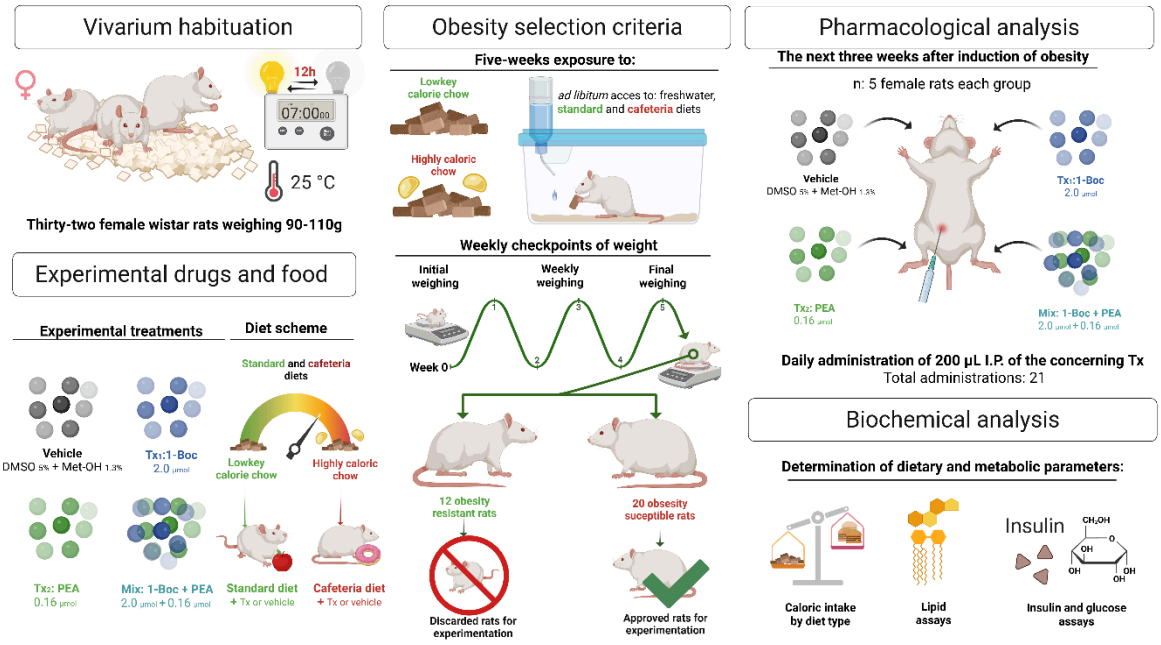


Figure 1. Rationale of the experimental protocol.

Results

Classification as obese-susceptible rats

Figure 1 shows the weekly body weight gain, expressed as a percentage change from initial weight, used to select rats susceptible and non-susceptible (resistant) to the cafeteria diet. The average body weight gain in the first week was 19.97%. Of the 32 animals tested, those with a weight gain below 19.97% were considered resistant to the diet (n=12). Rats whose weight gain during week 1

exceeded the mean were considered susceptible to the cafeteria diet (n=20).

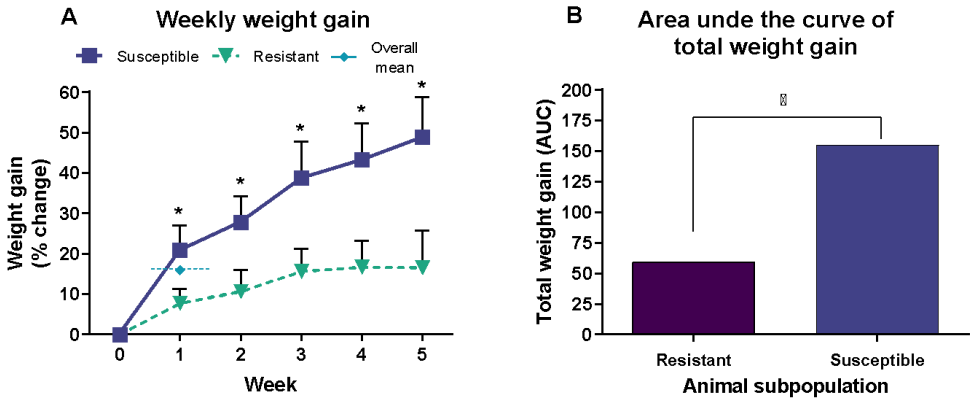


Figure 1. Weekly average cumulative body weight gain in rats with daily access to a cafeteria and standard chow diet. From 1 week media, rats were classified as resistant or susceptible. *, $p < 0.05$ vs. week 1 from the respective treatment. One way ANOVA was performance. Data are expressed as the mean ± SEM.

Pharmacological effect on body weight in rats susceptible to obesity

Figure 2 compares the effects of treating groups of animals susceptible to the cafeteria diet with Vehicle (5% DMSO + 1.3% methanol), 1-BOC (2 µmol), PEA (0.16 µmol), and Mix (PEA + 1-BOC - piperidine) on weekly body weight (expressed as percentage change in weight/21 days). These results indicate that PEA and 1-BOC - piperidine decrease the body weight of cafeteria-diet obese rats.

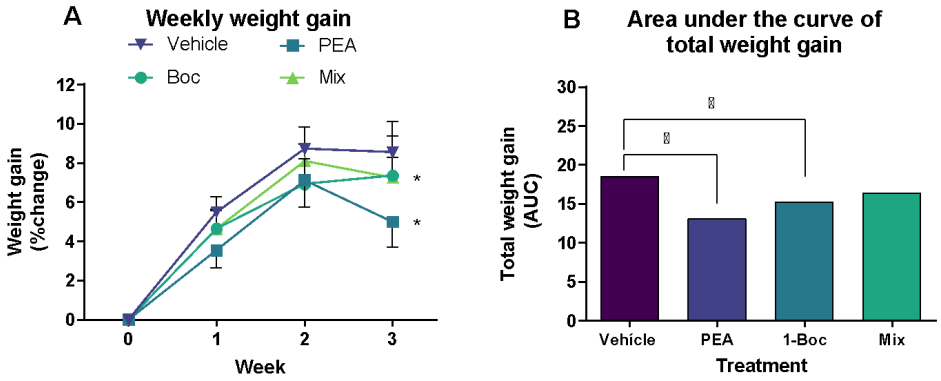


Figure 2. This shows the effect of the treatments: vehicle (DMSO 5%+1.3% methanol), 1-Boc (2µmol), PEA (0.16 µmol) and Mix (PEA+1-BOC-piperidine) on changes in body weight and area

under the curve (n=5 animals/group). Effect of treatments on body weight from obese rats. *, p < 0.05 vs. week 1 from the respective treatment. One way ANOVA was performed. Data are expressed as the mean ± SEM.

Effect on food preference in rats

Figure 3 shows the effects of different treatments on calorie consumption in rats fed standard food or cafeteria diet.

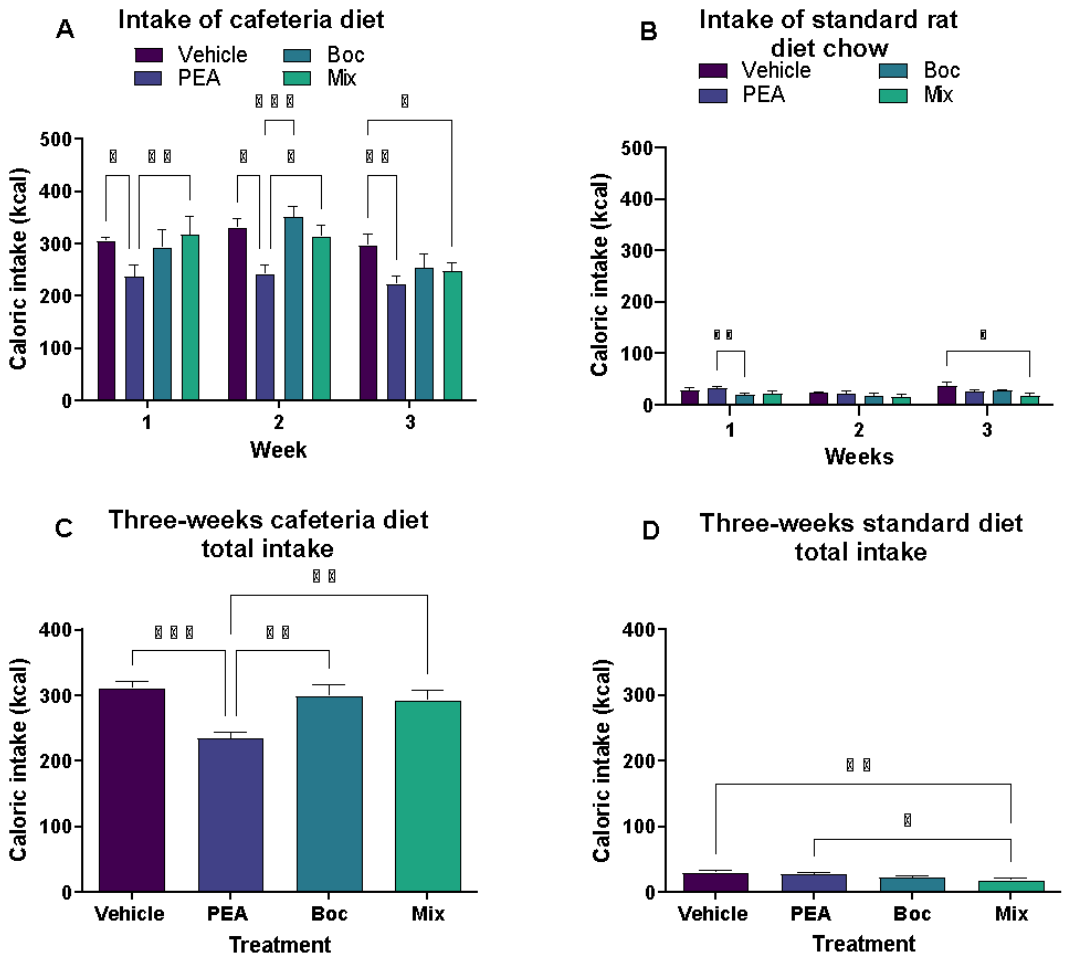


Figure 3. Weekly and total caloric intake of the standard food and cafeteria diet. Treatment in rats over 21 days. (A) shows the caloric intake of the cafeteria diet over three weeks, (B) shows the intake of the standard diet over three weeks, (C) and (D) show the total caloric intake of the cafeteria diet and standard diet respectively in the experiment, and (E) is the sum of the caloric intake from both diets ¿At the third week?. *P < 0.05 vs. the Vehicle group, #P < 0.05 vs. the PEA group, βP < 0.05 vs. week 1, αP < 0.05 vs. week 2.

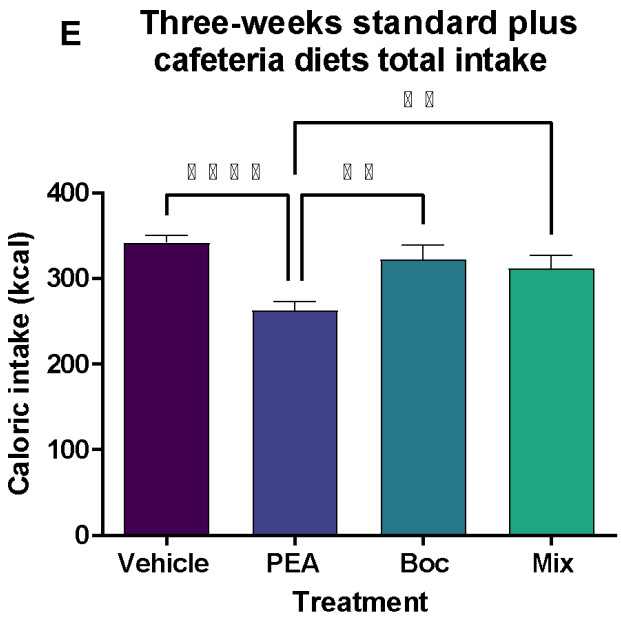


Figure 4. The sum of the caloric intake from both diets ¿At the third week?. *P < 0.05

Pharmacological effect on some biochemical parameters in the blood of obese rats

Biochemical analyses in the 'cafeteria diet' model were performed to compare the effect of 1-Boc-piperidine and PEA alone or in combination, on metabolic damage or protection in animals by studying total glucose, insulin, cholesterol, and triglyceride levels.

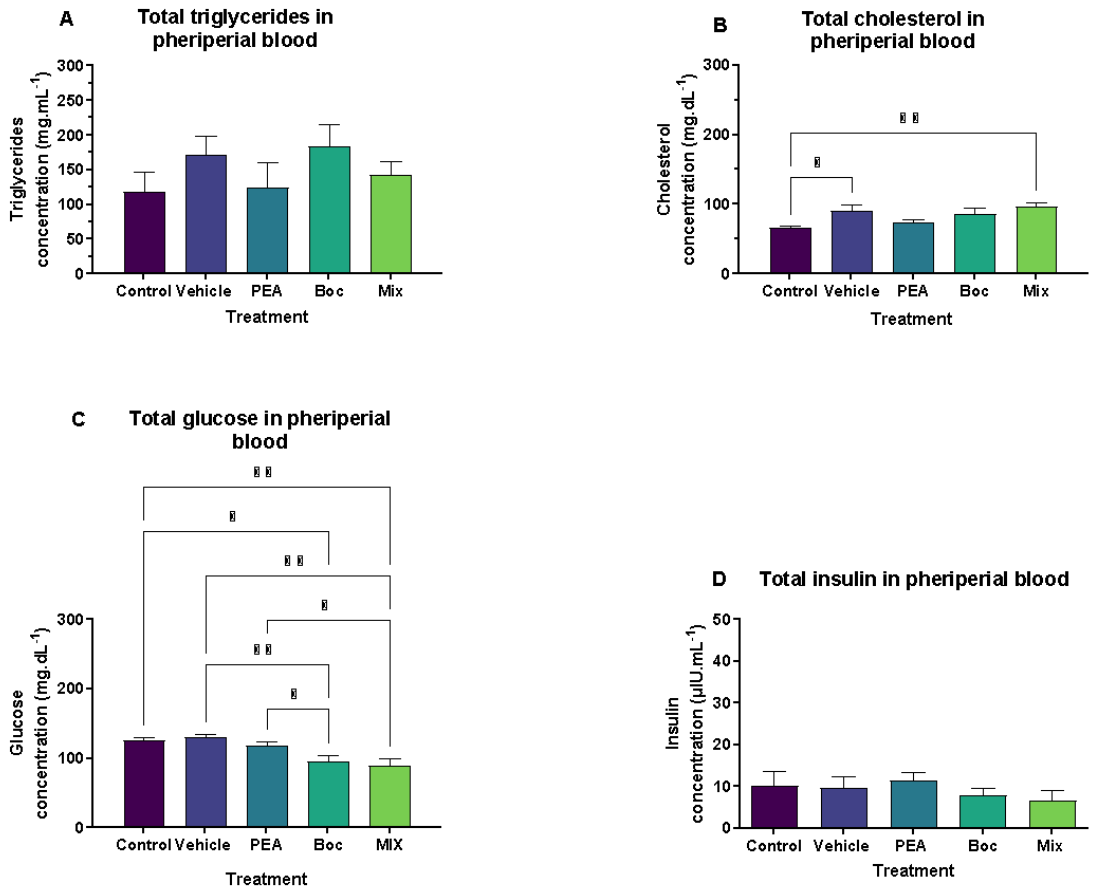
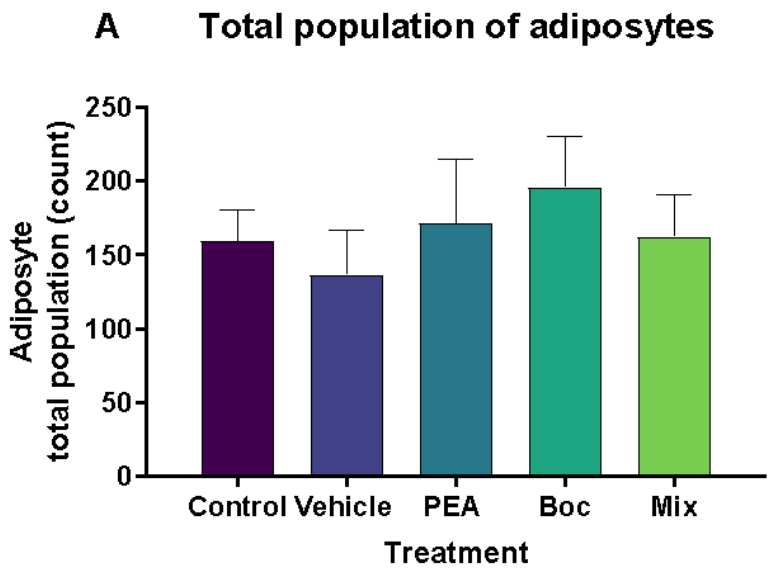


Figure 4. Biochemical analysis of the effect of 1-Boc-piperidine, PEA, and their combination on metabolism. The figure shows circulating blood levels of: A) triglycerides, B) total cholesterol, C) glucose, and D) insulin levels. ϕ $P < 0.05$ vs. the control group, *$P < 0.05$ vs. the vehicle group, #$P < 0.05$ vs. the PEA group.

Adipose cell parameters

The analysis of adipose tissue parameters was carried out to evaluate the possible metabolic effect of 1-Boc and palmitoylethanolamine on cell proliferation and increased cell size caused by a cafeteria diet.


A
Total population of adiposytes
Adiposyte total population (count)
250
200
150
100
50
0
Control
Vehicle
PEA
Boc
Mix
Treatment

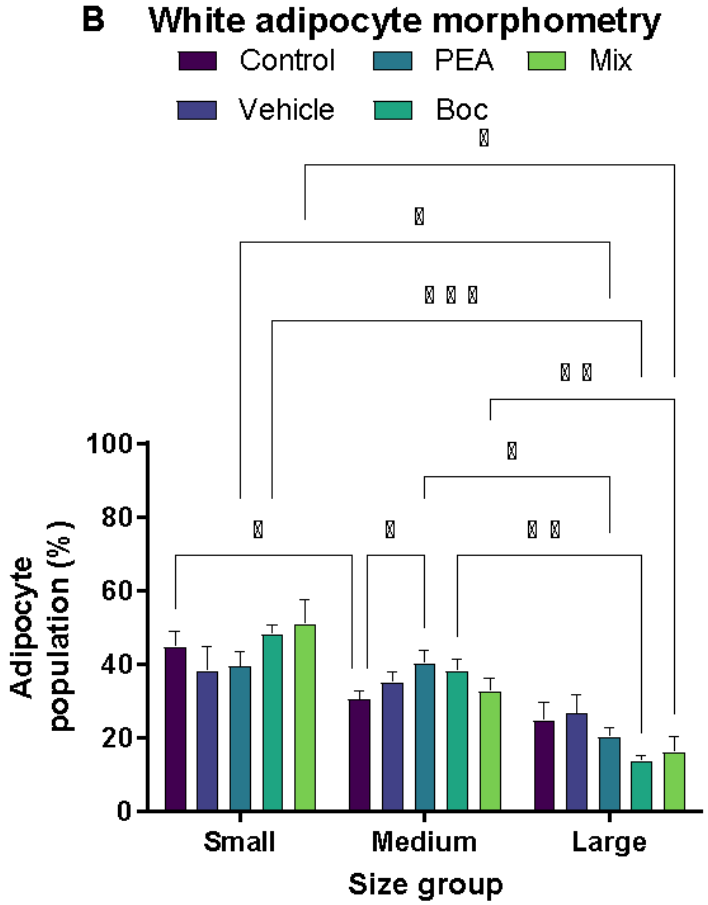

B
White adipocyte morphometry
Control
Vehicle
PEA
Boc
Mix
Adipocyte population (%)
100
80
60
40
20
0
Small
Medium
Large
Size group

Figure 5. Cellular analysis of adipose tissue after a hypercaloric diet (cafeteria diet). Figure A shows the percentage of different sizes (small, medium, and large) of adipocytes under the different treatments, suggesting 1-Boc as a possible lipid protector. Figure B indicates the total number of adipocytes in the groups with the different treatments.

Discusion

Raso et al, (Raso et al., 2014) and others found that ovariectomized rats given PEA ate less, lost weight, and lost fat mass. Researchers think that this is because leptin signals through phosphorylation of STAT3 in the hypothalamus. The obesity models are different (ovariectomy vs. cafeteria diet), but both studies use female Wistar rats and look at similar metabolic outcomes. Additionally, (Annunziata et al., 2022), reported that ultramicromized PEA administered to mice on a high-fat diet induced a transformation of white adipose tissue into a beige phenotype through the activation of PPAR-α. This resulted in the restoration of brown adipose tissue morphology and the reestablishment of thermogenic markers. The trend toward smaller adipocytes in the group that got 1-BOC in this study might be similar to the effects of remodeling adipocytes, but this is just a guess because there were no molecular studies to back it up.

Another key methodological point to think about is that methanol was used as part of the vehicle in this investigation. Methanol can be toxic at high doses, but the amount used in this study was much lower than the amounts usually used in experiments with rats that are meant to show how quickly methanol poisoning happens (Cejnar et al., 2022). Previous research has utilized doses of 3 g/kg as a non-fatal poisoning regimen, although the documented minimum lethal dose in rats is approximately 9.5 g/kg. In this case, it's unlikely that the very little amount of methanol given as a vehicle alone would explain the changes in body weight, food intake, or metabolic parameters that

were seen (Röe & Enoksson, 1982; Yazgan et al., 2017). However, a minor contribution cannot be completely ruled out, and this should be acknowledged as a methodological limitation of the study.

There is still not a lot of information on 1-BOC-piperidine in the literature, (Guzmán-Rodríguez et al., 2021), observed that this molecule diminished, in a dose-dependent way, the consumption of high-calorie foods during a binge-eating paradigm in female Wistar rats and exhibited an anxiolytic effect upon acute exposure.

(Matias et al., 2007) reported that PEA levels are significantly reduced in hypertrophic adipocytes and subcutaneous adipose tissue of diet-induced obese mice, indicating that PEA deficiency may contribute to the pro-inflammatory state associated with obesity. he reduction of triglycerides and modulation of glycemia observed in this study align with findings by (Tyurenkov et al., 2019), who reported that the GPR119 agonist ZB-16 curtailed weight gain and inhibited changes in carbohydrate metabolism in rats subjected to a hypercaloric diet, highlighting its significant role in insulin sensitization through AMPK

(Raso et al., 2014).

On the other hand, comparable studies show that the reduction in cafeteria diet caloric intake under 1-BOC is consistent with reports of GPR119 ligands in hypercaloric models (Overton et al., 2006; Tyurenkov et al., 2019).

Another plausible coincidence to corroborate with this study in the literature is that the tendency towards smaller adipocytes under 1-BOC could be associated with reduced adipocyte hypertrophy, documented in the PPAR-α/AMPK context (Annunziata et al., 2022).although this study differs in the sex of the rats since females were used.

On the other hand, this study agrees with the general direction of glucumetabolic changes compatible with the literature on GPR119 agonists, as well as their hypophagic properties. This cannot be contrasted with the effects of 1-Boc-piperidine, which lacks affinity for ligands or compounds related to pharmacodynamics and biological efficacy (Overton et al., 2006).

It is important to mention that, although the PEA +1-BOC combination did not show a clear synergistic effect for the different parameters, it could be interpreted as receptor saturation, or unforeseen pharmacodynamic interactions subject to limitations such as the n=5 of the group, sex, or the time of exposure to the treatment. In this context, there is limited literature, such as the case of background studies on the combination of GPR119 agonists where they did show favorable effects on reducing body weight, such as that reported by (Al-Barazanji et al., 2015) Al-Barazanji et al., where they administered metformin to diet-induced obese mice.

In contrast, rather than claiming that the present model has a universal effect on cafeteria diet-induced obesity, we agree with Raso et al.,(Raso et al., 2014) that the formulation with PEA and 1-Boc are important in modulating some components of the obesogenic phenotype, thus understanding its context.

The results of this study with 1-Boc-piperidine are in line with the physiological framework Yang et al.,(Yang et al., 2018), used to explain how GPR119 can be changed, but this interpretation is still indirect and not final.

Conclusión

El presente estudio demuestra que tanto la administración de PEA, como del ligando **1-Boc-piperidina** disminuyen significativamente la ganancia de peso en ratas hembra Wistar con predisposición a la obesidad inducida por una dieta de cafetería. Además, estos compuestos demostraron una capacidad integral para modular la homeostasis energética, reportada en una menor ingesta calórica y una mejora en marcadores bioquímicos como lo son triglicéridos y glucemia.

A nivel histológico, la tendencia hacia adipocitos de menor tamaño, particularmente bajo el tratamiento con 1-Boc-piperidina, sugiere que estos mediadores lipídicos podrían actuar como protectores contra la hipertrofia de adipocitos y promover un metabolismo favorable. Estos hallazgos refuerzan el papel de PEA y de los receptores **GPR119** como piezas clave en la restauración de la sensibilidad a la insulina en pro de la flexibilidad metabólica.

Finalmente, a pesar de no observarse un sinergismo claro en la combinación de ambos tratamientos en este modelo, los resultados demostraron un potencial terapéutico de estas moléculas en el manejo del modelo fenotípico de la obesidad. Futuras investigaciones con muestras más amplias y estudios mecanísticos directos serán esenciales para terminar de esclarecer las vías moleculares, como el browning o la activación del eje AMPK/PPAR, que refuercen o sustenten estos beneficios.

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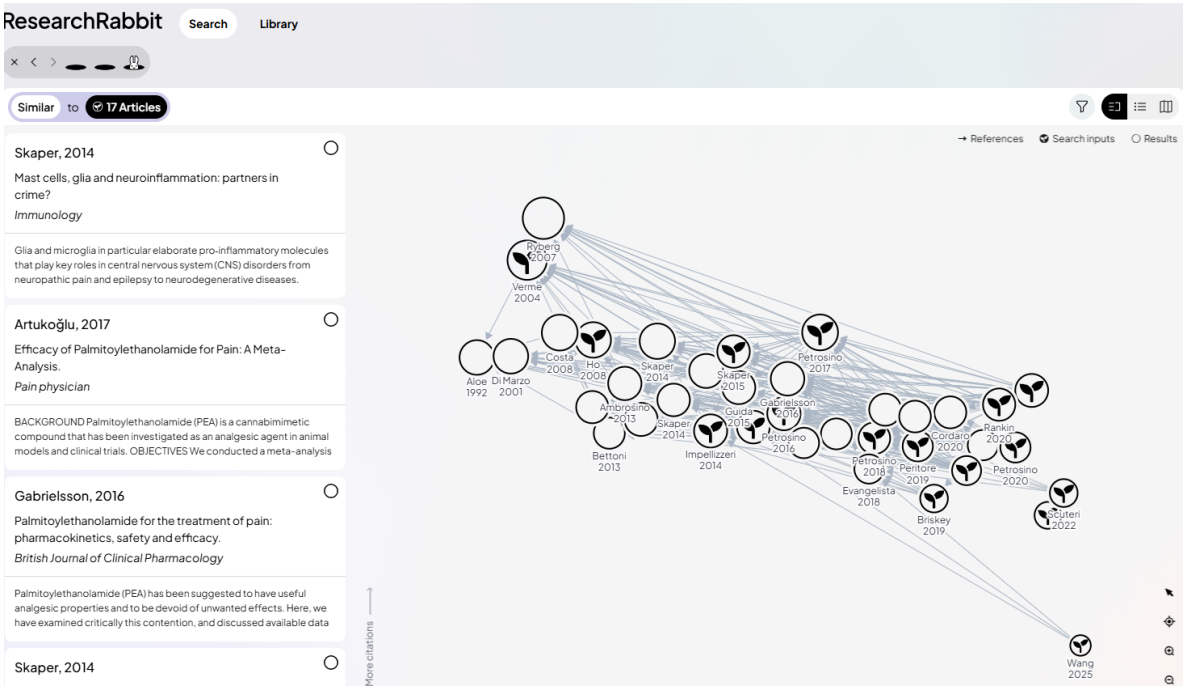
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