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Piceatannol affects fatty acid mobilization during isoproterenol-induced lipolysis in pig precision-cut adipose tissue slices

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ABSTRACT

Piceatannol, a stilbene structurally close to resveratrol, was previously shown to reduce lipolysis in mouse adipocytes both *in vitro* and *in vivo*. Here, we investigated the effects of both resveratrol and piceatannol on pig precision-cut adipose tissue slices stimulated with isoproterenol, a beta-adrenergic receptor agonist. Neither polyphenol affected glycerol release by adipocytes when applied at 10 or 100 μM. However, both compounds appeared to reduce glycerol release at 1 mM, suggesting a potential lowering effect on triglyceride hydrolysis at high concentrations. Since polyphenols may react with hydrogen peroxide, a by-product of the glycerol assay, we evaluated potential interferences with the assay. We found a dose-dependent reduction of the dye production by both polyphenols at 50 μM and above, particularly strong in the case of piceatannol. To circumvent this interference, we quantified the production of free fatty acids using gas chromatography-flame ionization detection in isoproterenol-stimulated precision cut adipose tissue slices, as free fatty acid levels are expected to increase concomitantly with glycerol release during the hydrolysis of triglycerides. Analysis confirmed that piceatannol at 1 mM significantly reduced fatty acid release from adipocytes in isoproterenol-stimulated precision cut adipose tissue slices. In contrast, resveratrol effects were no longer significant. In conclusion, this study shows that high concentrations of piceatannol, but not resveratrol, influence fatty acid mobilization in a distinct species and *in vitro* model. It also highlights the interferences of polyphenols with enzymatic kits commonly used to assess lipolysis, emphasizing the importance of validating such observations through gas chromatography-based free fatty acid analysis.

1. Introduction

Obesity is driven primarily by an energy imbalance that leads to excessive fat accumulation through adipocyte hypertrophy and/or hyperplasia. During prolonged overnutrition, hypertrophy is the predominant mechanism of fat mass expansion in humans [1]. Pathophysiological consequences of adipocyte hypertrophy include chronic low-grade inflammation, insulin resistance and hypoxia, contributing to obesity-related comorbidities such as type-2 diabetes, non-alcoholic fatty liver disease and cardiovascular disorders [2]. Pro-inflammatory cytokines, such as TNFα and IL-6, activate lipolysis, whereas insulin resistance diminishes the antilipolytic activity of insulin on white adipose tissue (WAT) [3,4]. The excessive and uncontrolled lipolysis in WAT promotes the accumulation of free fatty acids (FFA) into non-adipose organs, leading to organ-specific lipotoxicity [3]. Excessive lipolysis of WAT also plays a detrimental role in cancer-associated cachexia (CAC), a multifactorial syndrome characterized by progressive loss of adipose and skeletal muscle mass that cannot be reversed by nutritional support [5–8]. Research highlights the early and critical contribution of WAT atrophy, which not only precedes muscle wasting but also correlates with patient survival [9,10]. Preserving WAT mass and functional integrity, including adipocyte viability and metabolic flexibility, is therefore crucial for improving CAC outcomes. [6–8]. Identifying inhibitors that reduce excessive lipolysis represents a promising therapeutic strategy for both obesity and cachexia.

Piceatannol (3,3′,4′,5-trans-tetrahydroxystilbene; PIC), a metabolite and structural analogue of the well-studied resveratrol (RES), differs only by a hydroxyl group at the 3' carbon [11,12]. Found in grapes, sim fruit (*Rhodomyrtus tomentosa*), passion fruit seeds and blueberries [13,14], this polyphenol exhibits enhanced metabolic stability compared to RES, potentially amplifying its antioxidant, anti-inflammatory,

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List of abbreviations

ATGL - Adipose triglyceride lipase
BSA - Bovine serum albumin
CAC - Cancer-associated cachexia
cAMP - Cyclic adenosine monophosphate
CTRL - Control
DMEM - Dulbecco's Modified Eagle Medium
DMSO - Dimethyl sulfoxide
FAME - Fatty acid methyl esters
FBS - Fetal bovine serum
FFA - Free fatty acid(s)
FID - Flame-ionization detection
GC - Gas chromatography
GC-FID - Gas chromatography-flame ionization detection
H_2O_2 - Hydrogen peroxide
HSL - Hormone-sensitive lipase
IL-6 - Interleukin-6
LDH - Lactate dehydrogenase
MGL - Monoacylglycerol lipase
PCATS - Precision cut adipose tissue slice(s)
PKA - Protein kinase A
PIC - Piceatannol
RES - Resveratrol
SPE - Solid phase extraction
TNF-α - Tumor necrosis factor alpha
WAT - White adipose tissue

anticancer and cardio-protective properties [12,15,16]. Although less studied in obesity-related contexts, PIC has demonstrated anti-adipogenic and antilipogenic effects in adipose cell models [17,18]. It has also been shown to reduce lipolysis in both *in vitro* and *in vivo* mouse models, as opposed to RES, which showed no effect or even a pro-lipolytic effect [19–24]. This antilipolytic effect of PIC was recently challenged by other studies suggesting that PIC may stimulate basal lipolysis in obese estrogen-deficient mice and murine adipocytes [25,26]. To the best of our knowledge, the impact of PIC on lipolysis remains unexplored in other models or species.

Tissue culture provides an alternative to traditional cell culture, as it allows for the control of environmental conditions while preserving some *in vivo* features. Precision cut tissue slices conserve the three-dimensional complexity, intercellular interactions, and the structural and functional characteristics of whole organ, making them valuable tools for studying kidney, intestine, liver, or lung physiology [27–31]. However, this *ex vivo* technique has seen limited application in adipose tissue, due to inherent slicing challenges [32]. Recently, a precision cut adipose tissue slices (PCATS) model was successfully developed for northern elephant seals (*Mirounga angustirostris*) and subsequently adapted for pigs (*Sus scrofa domesticus*) [32]. Given their physiological, anatomical, and genetic similarities to humans, pigs serve as valuable biomedical models for studying various pathologies including obesity [33–35].

This study investigated the potential antilipolytic effect of PIC on isoproterenol-stimulated pig PCATS and compared it to RES. Initially, lipolysis was assessed by quantifying glycerol release in the culture medium using an enzymatic colorimetric test, as previously applied in murine models. However, observed interactions between the polyphenols and assay components required methodological adjustment. To ensure accurate evaluation, lipolysis was subsequently quantified directly through the analysis of FFA in the culture medium, using gas chromatography-flame ionization detection (GC-FID), a method that does not rely on enzymatic reactions.

2. Material and methods

2.1. Sample collection

Four female Aachen minipigs (*Sus scrofa domesticus*) from the UCLouvain experimental farm were sampled for the experiment. Pigs were slaughtered for herd management purposes and subcutaneous adipose tissue samples were aseptically collected *post-mortem* from the dorsal pelvic area. In accordance with EU Directive 2010/63/EU on the protection of animals used for scientific purposes, no ethical approval was required, as the animals were not sacrificed for scientific research. Still, the tissue was made available for *ex vivo* experimentation. Inner adipose tissue cores were obtained using 6-mm biopsy punches (Uni-Punch, Premier, Plymouth, MA, United States). Cores were placed in sterile, oxygenated medium at 25 °C. The medium, adapted from Debier et al. [32], consisted of Dulbecco's modified eagle medium (DMEM) with 1 g/L glucose (Gibco, Life Technologies, Carlsbad, CA, United States), 10 mM HEPES buffer (Life Technologies), and antibiotic-antifungal mixture (100 U/mL penicillin, 100 U/mL streptomycin, 250 ng/mL amphotericin, 1 mg/mL gentamycin (Life Technologies) and 40 U/mL nystatin (Sigma-Aldrich, Saint-Louis, MI, United States)).

2.2. PCATS preparation and culture

Tissues were transported to the laboratory and processed under aseptic conditions to produce 1 mm-thick PCATS using a compact device built for making thin slices of rat spinal cord (Mouse and Rat Spinal Cord Matrices, Ted Pella Inc., Redding, CA, United States). Six slices were placed in pre-weighed tubes containing 0.5 mL of sterile culture medium at 37 °C and subsequently weighed. The culture medium consisted of DMEM 1 g/L of glucose, 5 % (v: v) fetal bovine serum (FBS; Life Technologies), 2 % (w: v) fatty acid-free bovine serum albumin (BSA; Sigma-Aldrich), and an antibiotic-antifungal mixture (100 U/mL penicillin, 100 U/mL streptomycin, 250 ng/mL amphotericin, 50 μg/mL gentamycin and 40 U/mL nystatin). Slices and medium were transferred to 24-well culture plates, with an additional 0.5 mL of culture medium per well. Plates were incubated at 37 °C with 5 % CO_2 under constant agitation, as previously described [32].

After 2 h, the culture medium was removed and replaced with 1 mL of fresh medium to eliminate cell debris and shredded cell contents. After 18 h, the medium was withdrawn and replaced with the specified experimental medium.

2.3. Lipolytic treatment

Previous experiment from our group showed that PIC did not affect glycerol (analyzed with enzymatic assay) or FFA (analyzed with GC-FID) release under basal lipolysis conditions in pig PCATS (Fig. A in supplementary data). Therefore, the present work focused exclusively on isoproterenol-induced lipolysis. Six experimental conditions were tested in triplicate on four minipigs. For each pig, three conditions involved increasing concentrations of PIC (Selleck Chemicals, Munich, Germany) and three conditions involved increasing concentrations of RES (Sigma-Aldrich). Each condition was performed in triplicate, with six slices per well. Overall, the replication scheme was 4 pigs x 6 conditions x 3 replicates x 6 slices per well. Both polyphenols were initially dissolved at 10 mM in 1 % (v: v) dimethyl sulfoxide (DMSO; Sigma-Aldrich) and subsequently diluted in the previously described culture medium to achieve final concentrations of 10, 100 and 1000 μM, based on previously published data [21]. Tissue slices were incubated with the

resulting media for 24 h, after which the media were replaced with fresh media containing 1 μM isoproterenol and the corresponding polyphenol (Sigma-Aldrich) for an additional 12 h. Basal and induced lipolysis controls were run in parallel, with and without the DMSO vehicle (0.1 % DMSO) and without exposure to either polyphenol. The 12-h lipolysis was selected based on a preliminary study indicating that isoproterenol-induced lipolysis, assessed by glycerol release from pig PCATS not exposed to polyphenols, reached a maximum and plateaued after 12 h. These preliminary findings also demonstrated a significant increase in glycerol release when isoproterenol was added to the culture medium compared to basal lipolysis (Fig. 1).

2.4. PCATS viability

Slices viability was assessed using two minipigs. Lactate dehydrogenase (LDH) levels in the collected media were measured across the six experimental conditions and controls described in section 2.3, using the Cytotoxicity Detection Kit (LDH) (Roche, Sigma-Aldrich). In this case, the replication scheme was: 2 pigs x 6 conditions x 3 replicates x 6 slices per well. At the start of the culture, tissue slices were lysed with 1 % Triton X-100 (Sigma-Aldrich) as positive control. To account for initial slicing-induced damage, LDH released during the first 2 h was subtracted from the total LDH in PCATS at culture initiation, yielding an "LDH initial" value representing only non-damaged cells. LDH released after the first and second incubations was then compared to "LDH initial" to calculate a percentage of cell mortality.

2.5. Lipolysis assay – enzymatic test

Lipolysis was assessed by measuring glycerol levels in the culture media at the end of the experiment. Glycerol concentration was determined using an enzymatic glycerol assay kit (ab133130, Abcam, Cambridge, UK) and expressed as μmol per gram of tissue. The principle of the assay, based on three sequential enzymatic reactions leading to a colorimetric readout, is illustrated in Fig. 2.

2.6. Lipolysis assay – FFA analysis

Lipolysis was also assessed via FFA quantification in the culture media at the end of the experiment using gas chromatography-flame ionization detection (GC-FID).

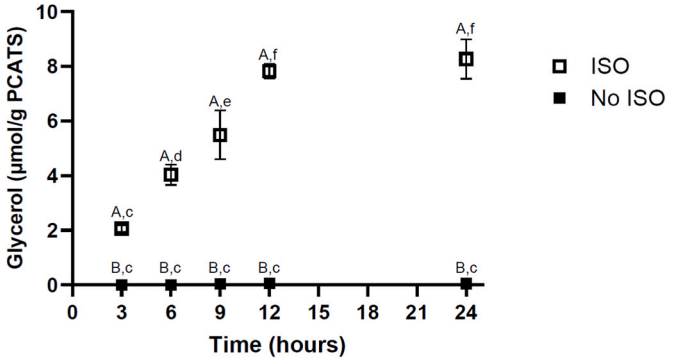

Fig. 1. Glycerol released over time from PCATS in response to a single isoproterenol (1 μM) treatment. Glycerol release in media was quantified using an enzymatic glycerol assay kit coupled to spectrophotometric (stimulated lipolysis) and fluorometric (basal lipolysis) measurements and normalized to the initial wet tissue weight. Results are expressed as mean ± SD of triplicate of one pig. Differences between conditions (stimulated vs basal) at a specific time point were analyzed with Student's t-tests. Differences between time points (3 h, 6 h, 9h, 12 h, and 24 h) within a condition were assessed using one-way ANOVA followed by Tukey's test. Values with different capital letters (A, B) are significantly different ($p < 0.05$) at a specific time point. Values with different lower cases (c, d, e, and f) are significantly different ($p < 0.05$) within a specific condition.

Total lipids were extracted from 0.8 mL culture media using a chloroform/methanol/water mixture (2:2:1, v:v:v) according to the Bligh and Dyer method [36]. Internal standard composed of nonadecanoic acid (Larodan, Solna, Sweden) was added to monitor the recovery of FFA. Due to the low FFA content in individual wells, total lipid extracts from two wells of the same experimental condition were pooled after the extraction step to ensure sufficient material for detection and quantification by GC. Total lipid extracts were separated into three lipid fractions: neutral lipids, phospholipids and FFA, by solid phase extraction (Bond Elut-NH_2, 200 mg, 3 mL silica based SPE column; Agilent technologies, Santa-Clara, CA, USA) [37]. To do so, total lipid extract dissolved in 200 mL of chloroform was loaded on columns Fig. 3 preconditioned with 3 mL of hexane. Neutral lipid, FFA and phospholipid fractions were eluted with 1.8 mL of chloroform–2-propanol (2:1, v:v), 2.4 mL of diethyl ether–acetic acid (98:2, v:v) and 1.8 mL of methanol, respectively. The phospholipid and neutral lipid fractions were discarded. The FFA fraction was dried under a stream of nitrogen (N_2) at 30 °C and methylated under alkaline condition (0.5 mL KOH/MeOH, 0.1 M at 70 °C for 60 min) followed by acidic condition (addition of 0.2 mL HCl/MeOH, 1.2 M, at 70 °C for 20 min). Resulting fatty acid methyl esters (FAME) were extracted using 1 mL hexane (adapted from Ref. [37]). An injection standard, i.e. methyl-undecanoate (Larodan), was added to all samples. FAME were separated by GC. The chromatograph (GC Trace-1310, ThermoFischer Scientific, Whaltam, MA,USA) was equipped with a Restek Rt-2560 capillary column (100 m × 0.25 mm internal diameter, 0.2 μm inner film thickness; Bellefonte, PA, USA), a TriPlus AS autosampler (Thermo Fischer Scientific, USA) and a flame ionization detector (FID; ThermoFischer Scientific) flowed by H_2 (35 mL/min), air (350 mL/min) and N_2 (40 mL/min) at constant temperature (255 °C). Samples were injected with H_2 as carrier gas at constant pressure (200 kPa) and flow rate (2 mL/min). The temperature program started with an increase from 80 °C to 175 °C at a rate of 25 °C/min. After 25 min at 175 °C, the temperature increased to 200 °C at a rate of 10 °C/min. After 20 min at 200 °C, the temperature increased to 220 °C at 10 °C/min. After 5 min at 220 °C, the temperature increased to 235 °C at 10 °C/min. After 15 min at 235 °C, the temperature decreased to 80 °C at 20 °C/min. Resulting chromatograms were analyzed with the ChromQuest software (version 5.0, ThermoFischer Scientific). FAME were identified and quantified by comparison of retention time and peak area with an external standard made from known concentrations of 42 FAME (Larodan).

Experiments were conducted using fatty acid-free BSA. Despite this, trace amounts of FFA potentially remained in culture media due to their presence in FBS. To account for this, FFA concentrations were measured in the media prior to PCATS exposure. These baseline values were subsequently subtracted from post-incubation FFA concentrations to correct for the initial FFA content. Baseline levels constituted less than 9 % and 21 % of the total initial FFA measured under conditions of low (0–100 μM PIC or RES) and high (1000 μM PIC or RES) lipolysis inhibition, respectively.

2.7. Statistical analysis

2.7.1. Statistical analyses and graphs were performed with JMP PRO 16 and GraphPad prism 9 software

Distribution normality and variance homoscedasticity were verified (Shapiro-Wilk test, Levene test). When necessary, data were log transformed to achieve normality. Type I error (α) was set at 0.05. Data are expressed as mean ± SD. Data for glycerol release over time were analyzed using Student's *t*-tests to compare conditions at specific time points. Differences between time points within each condition were assessed using one-way ANOVA followed by Tukey's post-hoc test. Data regarding glycerol release were analyzed by fitting a mixed effects model with the pig as random effect. Post hoc comparisons using Student's t-test with Bonferroni correction were made between the six

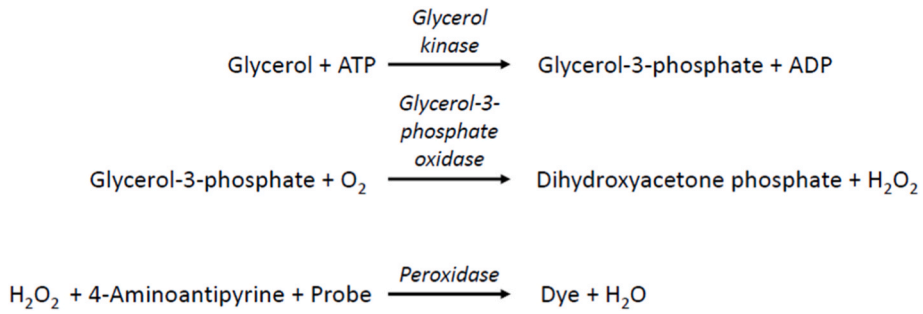

Fig. 2. Glycerol enzymatic assay principle.

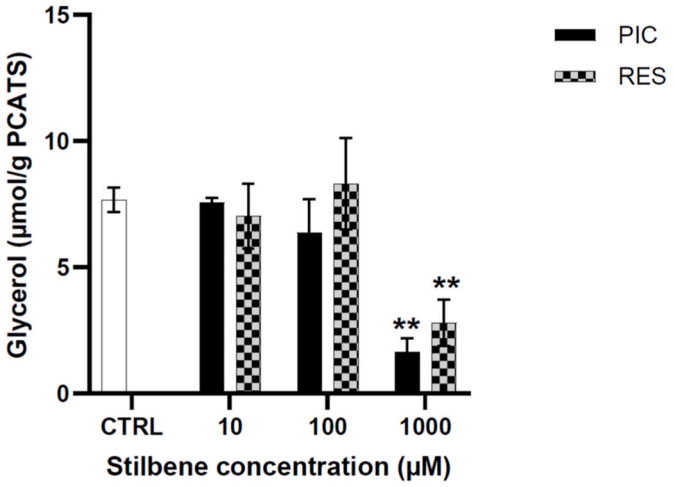

Fig. 3. Glycerol release in response to isoproterenol (1 µM) in PCATS incubated with piceatannol (PIC) or resveratrol (RES) at 10 µM, 100 µM and 1000 µM. Glycerol concentrations in media were quantified using an enzymatic glycerol assay kit coupled to spectrophotometric measurements and normalized to the initial wet tissue weight. Results are expressed as mean ± SD of four pigs. Differences between treatments were analyzed with a mixed model followed by Student's t-test with corrections for multiple comparisons. "*" and "**" indicate values significantly different from the vehicle control (CTRL = 0.1 % DMSO + ISO) at $p < 0.05$ and $p < 0.01$, respectively.

treatments and the control and for each concentration between the two polyphenols. Data regarding FFA release were analyzed with a linear regression. Post hoc comparisons using Student's t-test with Bonferroni correction were made between the six treatments and the control and for each concentration between the two polyphenols. Regarding polyphenol interaction, one-way analysis of variance followed by Tukey's test was used to assess the impact of the treatments on the measured glycerol release.

3. Results

3.1. Viability

PCATS viability was not significantly affected by varying concentrations of PIC and RES, with cell death estimates consistently below 11 % across all conditions (Table 1).

At 24 h, LDH release ranged from 0.7 ± 0.2 % (PIC 10 µM, Pig 1) to 8.8 ± 0.4 % (PIC 1000 µM, Pig 1). After 36 h of exposure, the highest cytotoxicity was observed with PIC at 1000 µM in Pig 1 (10.8 ± 0.6 %) and RES at 1000 µM in Pig 2 (9.6 ± 5.0 %).

Table 1
Cytotoxicity (mean ± SD) for each treatment after 24 h and 36 h incubation with PIC or RES in minipig 1 and 2.

Treatment	Minipig	Cytotoxicity after 24 h	Cytotoxicity after 36 h
CTRL	1	1.1 ± 0.3 %	7.6 ± 1.9 %
	2	3.4 ± 1.2 %	7.5 ± 2.1 %
PIC 10 µM	1	0.7 ± 0.2 %	1.5 ± 0.7 %
	2	2.6 ± 0.9 %	2.3 ± 0.9 %
PIC 100 µM	1	0.9 ± 0.1 %	3.1 ± 1.3 %
	2	2.4 ± 0.5 %	5.1 ± 2.0 %
PIC 1000 µM	1	8.8 ± 0.4 %	10.8 ± 0.6 %
	2	8.1 ± 2.0 %	9.0 ± 1.4 %
RES 10 µM	1	1.4 ± 0.9 %	1.3 ± 0.9 %
	2	4.1 ± 0.6 %	4.3 ± 1.4 %
RES 100 µM	1	1.8 ± 0.4 %	2.2 ± 0.5 %
	2	2.2 ± 0.6 %	8.2 ± 2.7 %
RES 1000 µM	1	4.8 ± 0.8 %	6.9 ± 0.3 %
	2	5.8 ± 1.9 %	9.6 ± 5.0 %

3.2. High concentration of PIC and RES apparently reduce the release of glycerol from pig PCATS

After 12 h of isoproterenol-induced lipolysis (1 µM), glycerol release did not differ between the control without DMSO (8.2 ± 2.07 µmol/g PCATS) and the vehicle control with 0.1 % DMSO (7.49 ± 1.95 µmol/g PCATS), confirming that DMSO had no specific effect on lipolysis (Fig. B in supplementary data). Basal lipolysis (1.60 ± 1.64 µmol glycerol/g PCATS) was significantly lower than induced lipolysis (p-value <0.0001), validating isoproterenol stimulation. Under induced lipolysis, 1000 µM PIC and RES seemed to significantly reduce glycerol release from 7.49 ± 1.95 µmol/g of tissue to 1.65 ± 0.98 and 2.80 ± 2.31 µmol/g of tissue, respectively. Lower concentrations of PIC and RES did not impair the lipolytic action of 1 µM isoproterenol on pig PCAT (Fig. 2). Data are presented as mean ± SD (n = 4).

3.3. PIC and RES interact with the enzymatic test used to quantify glycerol

Les et al. [21] suggested that PIC and RES can undergo oxidation in the presence of hydrogen peroxide (H_2O_2). Given that the enzymatic glycerol assay relies on H_2O_2 to generate a quantifiable signal via a reaction with a detection probe, the presence of PIC and RES could potentially interfere with the accuracy of the test. To evaluate this possibility, serial dilutions of PIC and RES were prepared and tested for potential assay interference.

When PIC was added to glycerol standard solutions (0, 0.3, 0.6 and 1 mM), the measured glycerol concentrations decreased proportionally to PIC concentration in the culture medium. At 10 µM, PIC had no significant effect on glycerol quantification. However, at 50 µM, PIC decreased the detection of glycerol by 57.1 ± 1.6 %, 35.2 ± 2.5 %, and 18.0 ± 4.5 % for the 0.3, 0.6 and 1 mM glycerol standards, respectively. This inhibitory effect was further enhanced at 100 µM PIC, reducing the

detected glycerol levels by 66.6 ± 1.0 %, 60.1 ± 2.0 %, and 42.2 ± 1.7 % for the same concentrations. The most pronounced interference was observed at 1000 μM PIC, which resulted in a 95.8 ± 0.3 % inhibition of glycerol detection in the 1 mM solution (Fig. 4A).

RES exhibited a similar interfering effect as PIC but to a lesser extent. At 100 μM, RES reduced the measured concentrations of 0.3 mM, 0.6 mM, and 1 mM glycerol by 25.9 ± 3.7 %, 15.4 ± 5.5 %, and 13.3 ± 1.8 %, respectively. At 1000 μM, RES further decreased the detected concentration of 1 mM glycerol by 42.1 ± 6.5 % (Fig. 4B).

3.4. High concentration of PIC reduces the FFA released from pig PCATS

Since both polyphenols interfered with glycerol quantification, we used a non-enzymatic non-colorimetric technique to assess the potential antilipolytic effect of PIC on pig PCATS. FFA released into the culture media were extracted and quantified using GC-FID. DMSO had no impact on the levels of FFA released by the slices triggered with isoproterenol during 12 h (17.30 ± 4.32 μmol FFA/g PCATS in the control without DMSO vs 16.38 ± 3.30 μmol FFA/g PCATS for the control with 0.1 % DMSO) (Fig. B in supplementary data). Basal lipolysis (3.68 ± 2.93 μmol FFA/g PCATS) was significantly lower than induced lipolysis (p-value = 0.0037).

Low and moderate concentrations (10 and 100 μM) of PIC and RES did not reduce FFA release into the media from PCATs after 12 h of induced lipolysis. However, at the high concentration of 1 mM, both polyphenols appeared to exert an antilipolytic effect by decreasing FFA release. The trend was, however, only significant for PIC, where a concentration of 1000 μM significantly reduced FFA levels from 16.38 ± 1.65 μmol/g of tissue to 5.06 ± 3.07 μmol/g of tissue (Fig. 5).

4. Discussion

This study investigated the effects of PIC and RES on isoproterenol-induced lipolysis in pig PCATS.

Isoproterenol, a non-selective β-adrenergic agonist, activates the lipolytic pathway, leading to adenosine monophosphate (cAMP) production and protein kinase A (PKA) activation. This cascade promotes the phosphorylation of key lipolytic regulators such as perilipin and hormone-sensitive lipase (HSL), facilitating triglyceride breakdown within lipid droplets. The sequential action of adipose triglyceride lipase (ATGL), HSL and monoacylglycerol lipase (MGL) ultimately results in the release of glycerol and FFA [4,38–40].

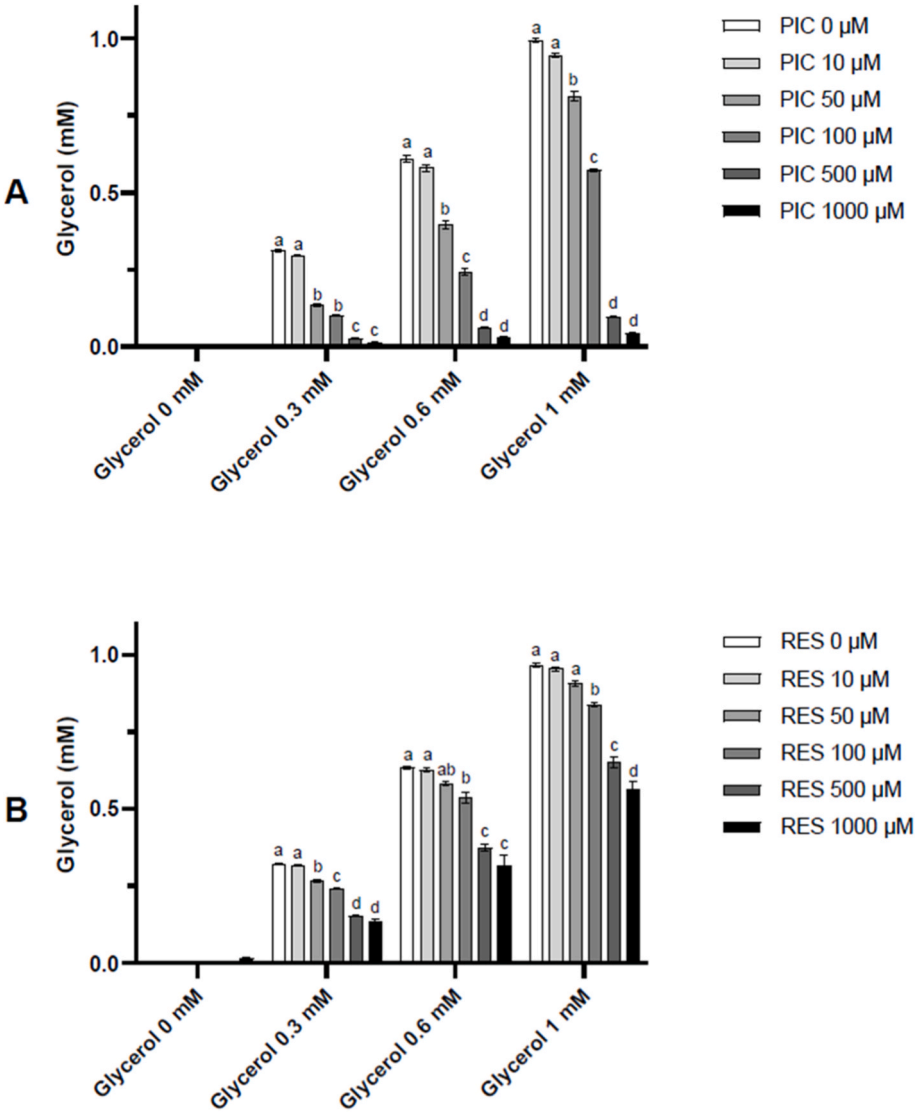

Fig. 4. Piceatannol (PIC) (A) and resveratrol (RES) (B) interactions with the Glycerol Assay Kit. Increasing doses of PIC (0-10-50-100-500-1000 μM) were incubated with increasing doses of glycerol (0-0.3-0.6–1 mM) in the presence of the enzymatic reaction mix. The 0 μM condition corresponds to the vehicle control (CTRL = 0.1 % DMSO). Results are expressed as mean ± SD (n = 4). For each glycerol concentration, values with no common letter are significantly different ($p < 0.05$).

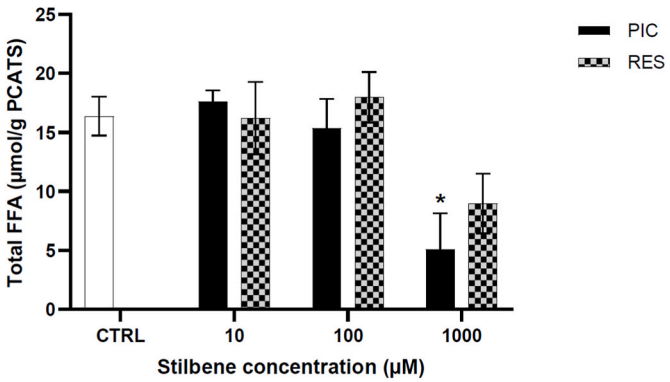

Fig. 5. FFA release in response to isoproterenol (1 µM) in PCATS incubated with piceatannol (PIC) or resveratrol (RES) at 10 µM, 100 µM and 1000 µM. FFA concentrations were quantified by GC-FID after lipid extraction and separation by SPE and normalized to the initial wet tissue weight. Results are expressed as mean ± SD of four pigs. Differences between the treatments were analyzed with a linear model followed by Student's t-test with corrections for multiple comparisons. "*" indicates values significantly different from the vehicle control (CTRL = 0.1 % DMSO + ISO) at $p < 0.05$.

Unlike FFA, glycerol cannot be re-utilized by adipocytes due to the absence of glycerol kinase in these cells [41]. Consequently, glycerol release into the extracellular medium is commonly used as a proxy for quantifying lipolysis with enzymatic glycerol assay kits. Most commercial glycerol assay kits rely on a coupled enzymatic reaction in which glycerol is first phosphorylated by glycerol kinase to generate glycerol-3-phosphate, which is in turn oxidized by glycerol-3-phosphate oxidase to produce dihydroxyacetone phosphate and hydrogen peroxide (H_2O_2) (Fig. 2). The H_2O_2 subsequently reacts with a chromogenic or fluorogenic probe in the presence of peroxidase, generating a colored or fluorescent compound whose absorbance or fluorescence can be measured.

This method has been previously used to investigate the impact of PIC and RES on lipolysis in both *in vitro* and *in vivo* mouse models [19–21]. However, studies indicated that both compounds are susceptible to oxidation in the presence of H_2O_2 [21,22]. Given that H_2O_2 is a key intermediate in the glycerol assay, we hypothesized that PIC or RES might compromise assay accuracy by potentially altering H_2O_2 levels. To test this, we assessed their impact on glycerol quantification by adding known amounts of each compound to standard glycerol solutions. Our results confirmed that PIC, and to a lesser extent RES, interfere with the assay in a dose-dependent manner. In addition to affecting H_2O_2 levels, it is also possible that PIC and RES directly interfere with the enzymatic components of the assay. Indeed, one study demonstrated that dietary antioxidants can disrupt the Amplex Red/horseradish peroxidase (HRP) reaction, suggesting a potential interaction with HRP itself [42]. Consequently, a similar interaction with the peroxidase present in the glycerol assay cannot be ruled out. Another study suggested that PIC may inhibit glycerol-3-phosphate dehydrogenase, based on its known inhibitory effects on glyceraldehyde 3-phosphate dehydrogenase [17]. It is therefore plausible that both polyphenols may also interfere with glycerol-3-phosphate oxidase, another key enzyme in the assay. Additionally, we observed that prolonged incubation with PIC, but not RES, resulted in a visible coloration of the medium, which may confound absorbance-based readings. However, this change in medium color did not occur under the conditions used to assess PIC and RES interference in the current study, as incubation times did not exceed 1 h. Further investigations are required to elucidate the precise mechanisms by which PIC and RES interact with the components of the glycerol assay.

Interestingly, while a 100 µM solution of PIC significantly interfered with the assay when applied directly in a simplified system (i.e. the interference test), the same concentration introduced into the culture medium containing the PCATS did not alter glycerol concentrations compared to the control. One plausible explanation for this apparent discrepancy is that PIC was likely partially absorbed by the PCATS, thus reducing its effective concentration in the culture medium. This absorption would decrease the free PIC available to interfere with the enzymatic assay, thereby masking its effects under these experimental conditions.

Similar interferences may also affect FFA quantification kits, which also rely on enzymatic reactions that generate H_2O_2 and a chromogenic product. Therefore, when assessing the effects of polyphenols such as PIC and RES on lipolysis, alternative quantification methods should be considered to ensure data reliability. To do so, FFA release into the culture medium after 12 h of lipolytic stimulation was quantified using a non-enzymatic, non-colorimetric method. Specifically, FFA were extracted and analyzed by GC-FID, a technique that is unaffected by enzymatic interference, sample coloration, or redox reactions. Under lipolytic conditions, the hydrolysis of 1 mol of triglyceride yields 1 mol of glycerol and 3 mol of fatty acids. Therefore, a theoretical FFA to glycerol ratio of 3:1 is expected. However, unlike glycerol, FFA can be reutilized by adipocytes and re-esterified with glycerol-3-phosphate, which is derived either from dihydroxyacetone phosphate, an intermediate of glycolysis, or from the glyceroneogenesis pathway. This metabolic recycling typically results in a FFA-to-glycerol ratio lower than three [43–45]. In our study, the observed ratios for PCATS in control conditions were close to two, indicating that a re-esterification process occurred during the 12-h lipolysis. Interpretation of these ratio values under polyphenol exposure was however not possible, given the underestimation of glycerol levels by the enzymatic assay.

The current study demonstrated that PIC significantly reduced the amount of FFA released into the medium by pig PCATS, by approximately two-thirds, a result consistent with previous findings on rodent models. Les et al. [21] were the first to suggest that PIC exerts an antilipolytic effect *in vitro* in murine adipocytes.Their assessment of lipolysis was however based on glycerol and FFA quantification using enzymatic kits, which we demonstrate here to be unreliable in the presence of PIC due to its interference with the assay, resulting in an artificially diminished glycerol signal. More recent studies, also relying on enzymatic assays, provided mechanistic insights into PIC's mode of action. Kwon et al. [20] demonstrated that PIC inhibits basal and stimulated lipolysis by promoting the degradation of ATGL, perilipin 1, and comparative gene identification-58 (CGI-58) proteins via an autophagy-lysosome-dependent pathway [20]. Conversely, other studies suggest that PIC may stimulate basal lipolysis through effects on HSL phosphorylation via GPER/PKA pathways in obese estrogen-deficient mice and murine adipocytes [25,26]. In the present study, because we did not quantify key lipolytic markers such as ATGL or HSL at either the transcript or protein level, the observed reduction in FFA release with PIC cannot be unequivocally attributed to a direct inhibition of lipolysis. An alternative explanation could be that PIC enhances FFA re-esterification, thereby reducing extracellular FFA levels independently of lipase activity.

In contrast to previous studies conducted in rodent cell culture models, the present study employed an *ex vivo* pig model, which is considered more physiologically relevant to human research due to the physiological, anatomical, and genetic similarities between pigs and humans [33–35]. The effective antilipolytic concentration of PIC in our study was 1 mM, comparable to that used by Les et al. [21], but higher than the 25–50 µM concentrations reported in Kershaw et al. [19] and Kwon et al. [20]. These differences may reflect species-specific and model-specific responses, variations in experimental design as well as the method used to quantify lipolysis (enzymatic assay vs fatty acid quantification by GC). The concentrations of PIC used were far above those achievable through a normal human diet and should therefore be regarded as supra-nutritional doses [46]. In pathological contexts such as obesity and CAC, intravenous administration could be considered; however, further investigation is required to determine physiologically

relevant and attainable levels.

Contrary to PIC, RES did not significantly affect isoproterenol-induced lipolysis, although a trend towards reduced FFA release was observed. This finding is consistent with the results from Les et al. [21], who reported no effect of RES on isoprenaline or IBMX-induced lipolysis in murine adipocytes. However, it contrasts with other studies reporting that RES can enhance isoproterenol-induced lipolysis in rodent and human models [22–24]. The divergent effects of RES on lipolysis may be attributed to differences in experimental conditions, cell/tissue types or species.

5. Conclusion

In summary, this study demonstrates that high, supra-nutritional concentrations of PIC markedly reduced the release of FFA in the culture medium of pig PCATS stimulated by isoproterenol, as measured by GC-FID, a method unaffected by the enzymatic or redox interferences posed by polyphenols that compromise the reliability of classical glycerol assays. Such lower FFA levels may result either from a direct modulation of lipolysis or from enhanced FFA re-esterification. In contrast, RES showed a non-significant trend. By using a physiologically relevant porcine model, this study strengthens the translational potential of PIC as a modulator of FFA release. The ability of PIC to attenuate excessive FFA release may hold therapeutic implications in both CAC, where preserving fat mass is crucial, and obesity, where reducing circulating FFA could mitigate lipotoxicity damage and improve metabolic health. Further studies including quantification of key lipolytic markers such as ATGL or HSL, larger sample sizes, experiments with varying durations, and physiologically relevant dosing are needed to confirm these results and further elucidate the molecular targets of PIC in adipocytes.

CRediT authorship contribution statement

Apolline Goudmaeker: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Aurélien Warnant:** Investigation. **Thomas Baily:** Data curation, Formal analysis, Investigation, Validation. **Laura Pirard:** Conceptualization, Data curation, Methodology. **Martin Deladrière:** Data curation, Formal analysis, Investigation. **Jean-François Rees:** Writing – review & editing. **Yvan Larondelle:** Writing – review & editing, Resources. **Cathy Debier:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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