VASODILATOR EFFECT OF OCTYLMETHOXYCINNAMATE ON HUMAN UMBILICAL ARTERIES

Juliana Felipe[1]

Ignacio Verde[2]

Abstract: Octylmethoxycinnamate (OMC) is a filter for ultraviolet B radiation used in sunscreens to protect skin. There is some evidence about the OMC activity as endocrine disruptor concerning a possible estrogenic activity, but its vascular effects were not still analyzed. The objective was to evaluate the non-genomic effects of the OMC on human umbilical artery (HUA) without endothelium. By mean of an organ bath system, HUA rings without endothelium were contracted by 5-hydroxytryptamine (5HT; 1μM) or by depolarization with KCl (60mM), and the effect of different concentrations of OMC was analyzed. The OMC elicits vasodilator effect on HUA without endothelium contracted by 5-HT (1μM) and by KCl (60mM). The effect was similar for the two contractile agents used. Here, we established that the OMC causes vasodilation of human arteries. This effect is analogous to the non-genomic effect caused by estradiol (E2), which occurs also by and endothelial-independent mechanism.

Keywords: Octylmethoxycinna-

1 Researcher at Health Sciences Research Centre (CICS-UBI) of the University of Beira Interior

2 Full Professor at the faculty of Health Sciences of the University of Beira Interior. Senior Researcher at Health Sciences Research Centre (CICS-UBI)

ISSN: 2763-5724
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mate, Endocrine disruptor, Human umbilical artery, Estrogen

INTRODUCTION

Endocrine disruptors are xenobiotics that can alter the normal functioning of the endocrine system and may affect the health of individuals exposed to them (Casals-Casas and Desvergne, 2011; De Coster and van Larebeke, 2012; Hampl et al., 2016; Nohynek et al., 2013). Octylmethoxycinnamate (OMC) is one of the most commonly used organic ultraviolet (UV) filters used in a number of cosmetic products (Hanson et al., 2015; Krause et al., 2012) at the maximum concentrations of 7.5% to 10% (Krause et al., 2012).

In the last years, a number of studies conducted with OMC have demonstrated their estrogenic activity (Gomez et al., 2005; Heneweer et al., 2005; Inui et al., 2003; Klammer et al., 2005; Schlumpf et al., 2001; Schreurs et al., 2002; Schreurs et al., 2005). Some authors shown effects of OMC on hypothalamic-pituitary--thyroid axis (Klammer et al., 2007; Schmutzler et al., 2004; Schmutzler et al., 2007) and also on neurotransmitter release in the central nervous system (CNS) (Carbone et al., 2010; Szwarcfarb et al., 2008). Regarding the estrogenic activity, in vitro studies showed that the OMC causes proliferation of MCF-7 breast cancer cells, exerting about 77.18% of the maximal effect observed with estradiol (E2), and with an EC 50 of 2.37μM (Schlumpf et al., 2001). Also in MCF-7 cell line, other authors demonstrated that OMC increases the expression of the pS2 gene (Heneweer et al., 2005).

The binding affinity for the estrogen receptor type alpha

(ERα) and type beta (ERβ) was also investigated (Gomez et al., 2005). The OMC revealed transactivation ability of ERα (Gomez et al., 2005; Schreurs et al., 2002), having been considered a weak ERα agonist (Schreurs et al., 2005). In vivo studies also demonstrate a dose-dependent uterotrophic effect in immature mice after oral ingestion of OMC (Schlumpf et al., 2001). In oophorectomized adult female rats, weight gain and increased expression of ERβ and C3 gene in the uterus were observed following oral administration of 10 to 1000 mg/kg/day for five days (Klammer et al., 2005). Also in this rat type, the ingestion of different amounts of OMC increased IGF-1 expression, the endometrium, myometrium and vaginal epithelium thickness (Seidlova-Wuttke et al., 2006a). The same authors showed a decrease in adipose tissue deposits, serum levels of leptin, triglycerides, serum cholesterol, LDL and HDL (Seidlova-Wuttke et al., 2006b)

OMC was detected in the plasma 1 to 2 hours after its topical application and exhibited urinary excretion, in the order of ng/mL (Janjua et al., 2008). The concentrations of this compound in plasma and urine are different in men and women, indicating a gender difference in the pharmacokinetics of this compound (Janjua et al., 2008). OMC was also detected in samples of human breast milk (Schlumpf et al., 2010).

Estrogens have a role in vascular tonus modulation, contributing to vascular smooth muscle relaxation (Cairrao et al., 2012; Smiley and Khalil, 2009; Watson et al., 2011). They act on estrogen receptors (ERs) that may be located intracellular-

ISSN: 2763-5724
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ly and modulate gene expression (genomic effects), or they may be located on the cell surface, quickly initiating the activation of several secondary messengers (non-genomic effects) (Watson et al., 2011). The non-genomic effects by estradiol (E2) can be due to high affinity binding and activation of a membrane receptor coupled to a G protein, the GPR30. This receptor may be located either in the endoplasmic reticulum or in the plasma membrane and may be responsible for rapid, non-genomic estrogen actions (Smiley and Khalil, 2009).

The binding of estrogens to the GPR30 receptor leads to the activation of Scr kinase and sphingosine kinase (SphK), which in turn activate matrix metalloproteinases (MMPs) (Prossnitz et al., 2008). MMPs cleave pro-heparan-bound epidermal growth factor (pro-HB-EGF) from the cell surface, releasing heparan-bound epidermal growth factor (HB-EGF). This leads to transcription of the epidermal growth factor receptor (EGFR) (Filardo et al., 2002; Prossnitz et al., 2008; Smiley and Khalil, 2009). EGFR initiates a series of cellular events, including the activation of phospholipase C (PLC), mitogen-activating protein kinase (MAPKs) and phosphatidylinositol 3-kinase (PI3Ks) (Prossnitz et al., 2008). The Gα-GTPase subunit activates adenylate cyclase, leading to the release of cyclic AMP (Filardo et al., 2002; Prossnitz et al., 2008; Smiley and Khalil, 2009). This secondary messenger, via protein kinase A (PKA), leads to the suppression of EGFR-induced Erk1/2 activity (Filardo et al., 2002; Smiley and Khalil, 2009).

No studies have yet been developed to assess the action of

the OMC in the cardiovascular system, but it is thought that it may have effects similar to those of estrogen. We aim to evaluate the rapid effects of OMC on the smooth muscle of HUA without endothelium, and to analyze whether these effects are similar to those elicited by estrogens.

2. METHODS

2.1. Extraction and preparation of human umbilical arteries (HUA)

Pieces of the umbilical cord (3–7 cm) were obtained from normal term pregnancies after vaginal delivery with the consent of the donor mothers. The procedures for the study have been approved by Ethics Committee of "Centro Hospitalar da Cova da Beira" (Covilhã, Portugal). The umbilical cord samples were collected in sterile physiological saline solution (PSS; composition mM: NaCl 110; CaCl2 0.15; KCl 5; MgCl2 2; HEPES 10; NaHCO3 10; KH2PO4 0.5; NaH2PO4 0.5; glucose 10; EDTA 0.49). To maximally reduce contamination and tissue degradation, we have added to the PSS penicillin (5 U/mL), streptomycin (5 µg/mL) and amphotericin B (12.5 ng/mL) and antiproteases (leupeptin 0.45 mg/L, benzamidine 26 mg/L and trypsin inhibitor 10 mg/L). We clean the adjacent connective tissue of HUA and cut HUA into 3–5 mm rings. The vascular endothelium was mechanically removed by introducing a cotton bud through the arterial lumen. The endothelium-denuded HUA rings were used to perform contractility experiments.

The rings were placed in DMEM medium (Dulbecco's Modified Eagle's medium) at 0-4 ° C for 24 hours and used for contractility studies.

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2.2. Artery contractility recording

Human umbilical artery rings without endothelium were placed in organ bath receptacles (LE01.004; Letica, Madrid, Spain) containing Krebs solution (composition in mmol/L: NaCl 119; KCl 5.0; NaHCO3 25; KH-2PO4 1.2; CaCl2 0.5; MgSO4 1.2; EDTA 0.03; ascorbic acid 0.6; glucose 11; pH 7.4) at 37ºC and gassed continuously with carbogen. The artery rings were suspended between two parallel stain-less steel wires and tension was measured using isometric transducers (TRI201; Panlab, Madrid, Spain) connected to an ML118/D Quad Bridge amplifier (ADInstruments, Oxford, UK), a PowerLab/4SP ML750 interface (ADInstruments) and a computer with Chart5 PowerLab software (ADInstruments). Isometric tension was measured in milligrams (mg) of force. Initially, the rings were equilibrated for 60 min by changes in the bath solution every 15 min, until a resting tension of 1.5g was achieved.

The HUA rings contractility was induced by 5-hydroxytryptamine (5-HT; 1 µM), or KCl (60mM). For the contractions induced by KCl, a modified depolarizing Krebs solution (composition in mmol/L: NaCl 69; KCl 60.0; NaHCO3 25; KH2PO4 1.2; CaCl2 0.5; MgSO4 1.2; EDTA 0.03; ascorbic acid 0.6; glucose 11; pH 7.4). To determine the rapid effects of OMC, the HUA rings were contracted by one of the contractile agents (5-HT or KCl) and, after obtaining the maximal contractile effect (plateau phase of the effect), increasing concentrations of OMC (1nM-50µM) were added to analyse the OMC effect on contractility. For this

OMC effect, we considered the percentage of reduction on maximal contraction induced by 5-HT or KCl. During the resting periods, the organ bath solution was changed every 15 min for period of 60-90 min. Control experiments with ethanol, the vehicle used to dissolve OMC, were always performed. The amounts of ethanol (3.4nM-170µM) were that present to prepare each dose of OMC. The maximal amount of ethanol present in the organ bath did not exceed 0.01%.

2.3. Drugs and chemicals

The drugs and chemicals were purchased from Sigma--Aldrich Química (Sintra, Portugal), excepting OMC (ACROS Organics- Thermo Fisher Scientific, Geel, Belgium). To prepare the initial stock solution of OMC we used ethanol as solvent, and afterwards we perform dilutions with water to prepare more eluted concentrations.

2.4. Statistical analysis

The data are expressed as the mean ± SEM of n experiments. Data were analyzed using SigmaStat Statistical Analysis System version 2.00 (Systat Software Inc., London, UK). We analyzed the differences between two groups by using Students t-test. Probability levels lower than 5% were considered significant ($P<0.05$).

3. RESULTS

The HUA rings without endothelium were contracted with 5-HT (1µM) and KCl (60mM), obtaining stable contractions after 5 to 10 minutes. The mean maximum contraction obtained with 5-HT and KCl is shown in Table 1. The maximal

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contractility elicited by both agents was not significantly different ($p>0.05$)

Table 1: Maximum contractile response induced by 5-HT (1µM) and by KCl (60mM) in HUA. Data are expressed as mean ± S.E.M.

Contractile agent	Contraction force (mg)
5-HT (1µM)	1615 ± 172
KCl (60mM)	1907 ± 190

After reaching maximal contraction, HUA were submitted to increasing concentrations of OMC (1nM-50µM) for approximately 5m intervals, time necessary to have a stabilized effect. Control procedures were performed simultaneously with ethanol, the vehicle used to dissolve the OMC. The effects observed were reversible since, after washing with Krebs solution, they were reversed.

3.1. Effects of OMC on 5-HT--induced HUA contractility

OMC exerted a significant relaxing effect on 5-HT-contracted HUA, whose maximum effect occurred at the concentration of 50µM, with a maximal relaxant effect of 19,48±4,23% (Fig. 1).

Ethanol, the vehicle to dissolve the OMC, did not induce any significant effect on 5-HT-induced contractions (Fig. 1). The

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effect observed with OMC was significantly different than that observed in the presence of ethanol at concentrations of 10 and 50 µM ($p<0,05$, Student´s t test).

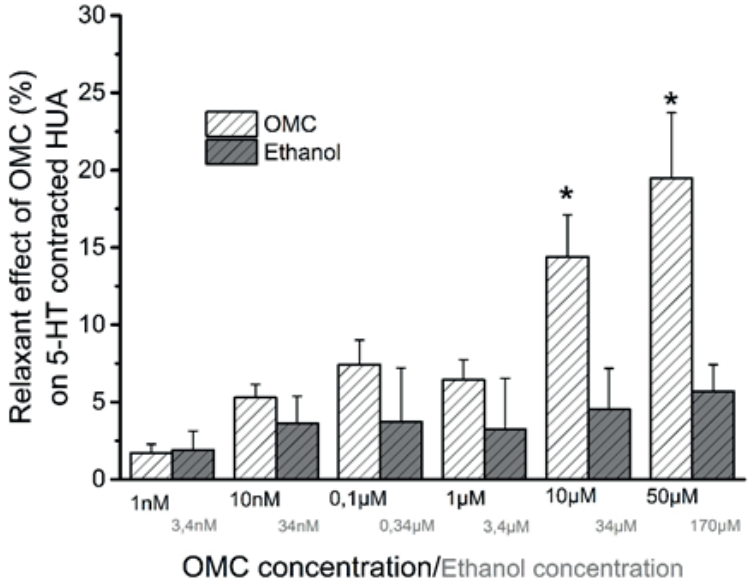

Figure 1: Relaxant effect (%) of OMC (1nM-50µM) on HUA maximal contraction elicited by 5-HT (1µM) As control, we used the amounts of ethanol (3.4nM-170µM) present to prepare each dose of OMC. Bars are the media od percent of relaxation on 5-HT maximal contraction and vertical lines are the S.E.M. *$p<0,05$ respective to control with ethanol (Student´s t test).

3.2. Effects of OMC on KCl-induced HUA contractility

OMC elicited a signi-

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ficant relaxant effect on KCl--induced contractions of HUA, with a maximal relaxant effect of 23,29±3,91%.

Ethanol, the vehicle to dissolve the OMC, did not induce any significant effect on KCl-induced contractions (Fig. 2).

The effect observed with OMC was significantly different than that observed in the presence of ethanol at concentrations of 0.1, 1, 10 e 50µM ($p<0,05$, Student t test).

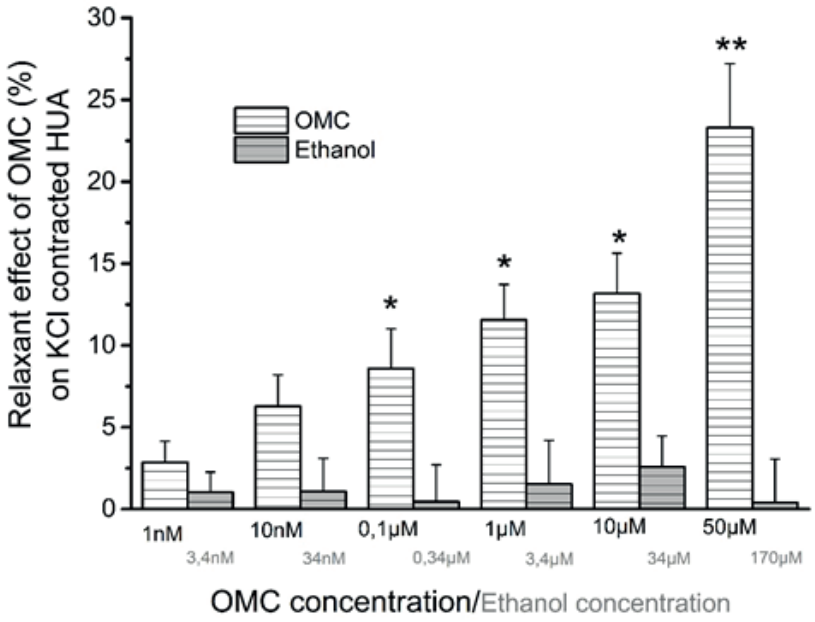

Figure 2: Relaxant effect (%) of OMC (1nM-50µM) on HUA maximal contraction elicited by KCl (60mM). As control, we used the amounts of ethanol (3.4nM-170µM) present to prepare each concentration of OMC. Bars are the media od percent of relaxation on KCl maximal contraction and vertical lines are the S.E.M. *$p<0,05$, **$p<0.01$, respective to control with ethanol (Student´s t test).

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The relaxant effect on HUA reached at each concentration of OMC used was similar for the two contractile agents, 5-HT and KCl ($p>0,05$, Student´s t test; Fig. 3).

However at the concentration of 1µM of OMC, the relaxation is nearly significantly bigger ($p=$ when the arteries were contracted with KCl compared with that contracted by 5-HT.

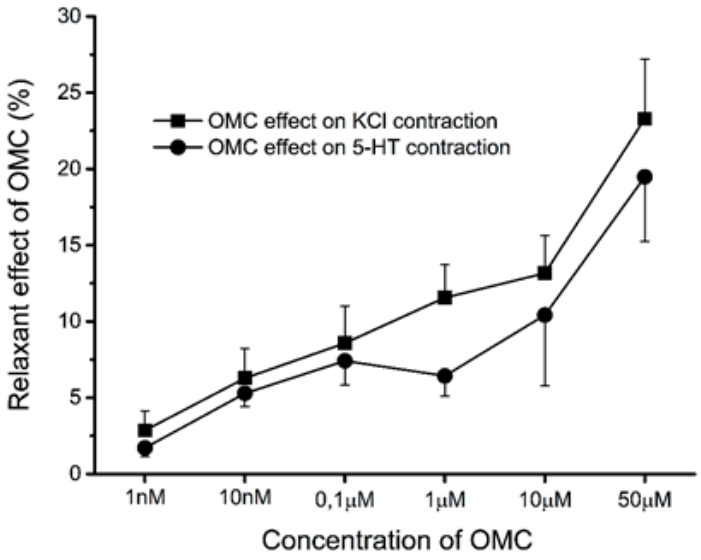

Figure 3: Relaxant effect of OMC (%) on HUA contraction elicited by 5-HT (1µM; n=8) and by depolarization with KCl (60mM; n=9). Each point represents the media and vertical lines are the S.E.M

DISCUSION

In our study, we evaluated the effect of the OMC on HUA without endothelium. The data demonstrated that the OMC exerted a relaxant vasodilatory effect both on the 5-HT and KCl--contracted HUA, with maximal effects at 50µM. The degree of relaxing response obtained was

ISSN: 2763-5724
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similar regardless of the contractile agents used.

In the classical genomic pathway, once ERs is activated it acts as transcription factor, modulating gene expression (Smiley and Khalil, 2009). At the vascular level, estrogens also exert non-genomic effects leading to vessel-relaxation (Cairrao et al., 2012; Smiley and Khalil, 2009; Watson et al., 2011). Regarding the OMC, some authors have tried to link their action as a possible endocrine disruptor by assessing their potential estrogenic effect at the genomic level. Thus, effects on proliferation, and increased gene expression were observed (Heneweer et al., 2005).

The mechanism of action by which the OMC can exert its estrogenic effects is not well known. The binding affinity of the ERα and ERβ recep0074ors was investigated, and OMC was characterized as a weak ERα agonist (Gomez et al., 2005; Schreurs et al., 2002), but also as a potent antagonist of progesterone receptors (Schreurs et al., 2005). Additionally, ERα transactivation ability was observed at concentrations of 0.1 and 10 µM of OMC (Gomez et al., 2005). However, other authors showed the presence of ERα gene transcript at high concentration of OMC (100 µM) (Schreurs et al., 2002).

However, some investigations suggest that the OMC may not exert an estrogenic effect. Morohoshi et al. (Morohoshi et al., 2005) did not detect any estrogenic activity of OMC, namely the binding to ERs that was by ELISA method (Morohoshi et al., 2005). Perhaps these authors used an inadequate estrogen concentration (below 100 µM), because other author only found antiestrogen activity of OMC at

100µM in an assay with yeasts expressing human ERα (Kunz and Fent, 2006). Given the contradictory findings of these authors, we can also hypothesize that OMC may exert the effects by other mechanisms not directly related to ERs.

Non-genomic effects are responses that occur too short to be mediated by genetic transcription, and are independent of protein synthesis (Smiley and Khalil, 2009). Some author suggested that estrogens vasodilator effect is due to the activation of kinases and phosphatases that alter ionic flux across the plasma membrane, and that the vasodilator effect of OMC can be dependent or independent of the endothelium (Smiley and Khalil, 2009).

A study also performed in HUA found that E2 relaxed the arteries by about 25-29%, with maximal effect at the concentration of 100µM (Fausett et al., 1999). In addition, in human epiploic arteries, a vasodilator effect of E2 at low concentration (3µM) has been described as being endothelium independent (Belfort et al., 1996). A study conducted by our research group demonstrated that E2 exerts an endothelium-independent vasodilator effect in rat aortic arteries at concentration equal or superior to 10µM (Cairrao et al., 2012).

Taking into account the results obtained in this study, we observe that OMC triggers the vascular relaxation in a manner similar to E2, by a non-genomic mechanism and independent of the endothelium.

The modulation of the ion channels is one of the pathways involved in non-genomic actions of estrogens. In fact, in vascular smooth muscle cells from rat aorta, estrogen inhibits

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L-type Ca2+ channels (Cairrao et al., 2012).

In the last decade, the GPR30 receptor was target of several studies on rapid effects of estrogens. This receptor is a G protein-coupled receptor with high affinity for E2. Once activated, it can present two distinct mechanisms of action, with opposite effects on the pathways concerning EGFR-MAPKs (Filardo et al., 2002; Smiley and Khalil, 2009). However, there are no published data regarding the analysis of this mechanism of action at the vascular level. Although a recent study in the smooth muscle of rat mesenteric arteries, demonstrated that the action of the GPR30 agonist, G-1, led to a vasodilator effect, the mechanism involved was the activation of adenylate cyclase and the increase of cyclic AMP levels in smooth muscle cells (Lindsey et al., 2014).

There are no published studies regarding the effect of the OMC at the vascular level or studding the possible involvement of OMC, as an endocrine disruptor, in the development of cardiovascular diseases. Thus, this study is pioneer in this regard, although further studies need to be performed to see if OMC can act on the GPR30 receptor or in other target. Maybe the binding of OMC to GPR30 could trigger an increase of cyclic AMP in the vascular smooth muscle cells, which could trigger the vasodilator effect.

In conclusion, this study demonstrated that the OMC has a rapid and endothelial-independent vasodilator effect. This effect is similar to that elicited by estrogens in the same artery. Additional studies are needed to evaluate the cellular and molecular changes that lead to the vessel

relaxation induced by OMC.

ACKNOWLEDGEMENTS

The authors would like to thank the donor mothers and the staff of the Gynaecology–Obstetrics Department of the "Centro Hospitalar da Cova da Beira" (Covilhã, Portugal) for their collaboration and Prof. Elisa Cairrão for the support given to the young researchers to learn the vascular contractility technique. This work was supported by FEDER funds, through the POCI-COMPETE 2020-Operational Programme Competitiveness and Internationalisation in Axis I-Strengthening research, technological development and innovation (Project POCI--01-0145-FEDER-007491) and National Funds by FCT-Foundation for Science and Technology (Project UID/Multi/00709/2013).

Conflicts of interest

The authors declare no conflict of interest.

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ISSN: 2763-5724
Vol. 01 - n 02 - ano 2021
Editora Acadêmica Periodicos

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