Activation of Peroxisome Proliferator Nuclear Receptors Regulates Lipid Metabolism in the Placenta

Alicia **JAWERBAUM**, Evangelina **CAPOBIANCO**, Nora **MARTINEZ**, Verónica **WHITE**, María Carolina **PUSTOVRH**, Romina **HIGA**, Elida **GONZÁLEZ**

Laboratory of Reproduction and Metabolism, CEFYBO-CONICET. School of Medicine, University of Buenos Aires, Buenos Aires, Argentina

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Abstract

Objective: Peroxisome proliferator activated receptors (PPARs), known regulators of lipid homeostasis in different tissues, are crucial during placental development. In this work, we aim to determine whether PPARs activation modulates lipid metabolism in the placenta from control and diabetic experimental models at midgestation.

Materials and Methods: Placental explants obtained from control and neonatal-streptozotocin-induced- diabetic rats on day 13.5 of gestation were cultured in the presence or absence of ligands of the three PPARs isoforms (clofibrate, 15-deoxyδ ^{12,14} prostaglandin J_2 and carbaprostacyclin; which are PPARα, PPARγ and PPARδ agonists respectively) for further analysis of lipid metabolism. Lipid levels (triglycerides, cholesterol, cholesteryl esters and phospholipids) were analysed by thin layer chromatography, *de novo* lipid synthesis was assessed by incorporation of ^{14}C-acetate as a tracer, and lipid catabolism was studied through the evaluation of glycerol release.

Results: Placental tissues from diabetic rats showed increased triglycerides and cholesteryl ester levels, decreased *de novo* lipid synthesis and enhanced lipid catabolism when compared to controls. PPARα activation reduced lipid levels and synthesis, and increased lipid catabolism in the placenta. PPARγ activation did not modify placental lipid mass and catabolism, but significantly reduced *de novo* lipid synthesis. PPARδ ligands reduced phospholipid levels and *de novo* lipid synthesis, and increased placental lipid catabolism.

Discussion: These results provide evidence of novel PPARs functions as regulators of placental lipid metabolism, a first step in the understanding of pathways that may allow the regulation of placental lipid metabolism and the prevention of the lipid overload transferred to the developing fetus in maternal diabetes.

Keywords: diabetes in pregnancy, placenta, lipids, peroxisome proliferator activated receptors

Özet

Hücre Çekirdeğinde Peroksizom Çoğaltıcı Reseptörlerin Hareketlendirilmesi Plasentada Lipid Metabolizmasını Düzenliyor

Amaç: Peroksizom çoğaltıcı hareketlendirilmiş reseptörleri (PPAR), değişik dokularda lipid dengelerinin bilinen düzenleyicileri olup, plasenta gelişmesinde çok önemlidirler. Bu çalışmada, PPAR hareketlendirilmesinin normalde ve şeker hastalığında plasentada lipid metabolizmasını değiştirip değiştirmediğinin saptanması amaçlanmıştır.

Materyal ve Metot: Neonatal-streptozotosinle şeker hastalığı oluşturulan sıçanlar ve normal kontrollerden gebeliğin 13.5'inci günü alınan plasentalarla kültür yapıldı. Kültürlere PPAR'nin üç benzer türü olan PPARα, PPARγ ve PPARδ'ya bağlanarak hareketlendirilen klorofibrat, 15-deoksiδ^{12,14} prostaglandin J_2 ve karbaprostasiklin katılarak veya katılmayarak lipid metabolizması incelendi. Trigliseridler, kolesterol, kolesteril esterleri ve fosfolipidlerince tabak kromatografisi ile ayrılarak ölçüldüler, *de novo* lipid sentezi ^{14}C-asetat izleyici bağlanması ile saptandı ve lipid katabolizması gliserol salınım ile ölçüldü.

Sonuçlar: Şeker hastalığı oluşturulan sıçanların plasentalarında trigliseridlerin ve kolesteril esterlerinin düzeyi yüksek ancak *de novo* lipid yapımı ve lipid katabolizması kontrollere kıyasla düşüktü. PPARγ hareketlendirilmesi plasentada lipid kütlesini ve katabolizmasını değiştirmedi ancak *de novo* lipid yapımını önemli ölçüde azattı. PPARδ bağlayıcılar, fosfolipid düzeyini ve *de novo* lipid yapımını azalttılar ve plasentada lipid katabolizmasını yükselttiler.

Corresponding Author: Dr. Alicia Jawerbaum
Paraguay 2155, 17th Floor 1121 Buenos Aires, Argentina
Phone : +54 114 508 36 80/109
GSM : +54 155 428 56 96
E-mail : a.jawerbaum@abaconet.com.ar

Tartışma: Sonuçlar, PPAR'lerin plasentada lipid metabolizmasının düzenlenmesini etkilediğini kanıtlamaktadır. Bu, metabolizma düzenleyici yolların anlanmasında bir ilk adım olup, hem bu yolların meydana çıkarılmasında hem de annede şeker hastalığı durumunda fetusa yüksek lipid yükü geçirilmesini önlemekte yararlı olabilir.

Anahtar sözcükler: gebelikte şeker hastalığı, plasenta lipidleri, peroksizom çoğaltıcı hareketlendirilmiş reseptör

Introduction

The placenta is an essential organ that transports the needed nutrients and oxygen from the mother to the fetus. Developmental, functional and structural anomalies in the placenta from diabetic pregnancies are considered in part responsible for several fetal complications that arise in this pathology (1).

In diabetic pregnancies, fetal overgrowth or macrosomia are consequences of increased maternal glucose, which stimulates fetal insulin production (2). Combined with the permissive environment of fetal hyperinsulinemia, excessive availability of different maternal nutrients to the placenta has been related to increased fetal adiposity and overgrowth (3). Indeed, there is a correlation between the maternal serum lipid levels and the fetal lipid accretion in diabetic pregnancies, an alteration related with both macrosomia and the intrauterine programming of glucose intolerance in the neonate (4,5).

Lipid transfer to the developing fetus is highly regulated within the placenta. Although there is no direct transfer of esterified lipids from maternal to fetal circulation, lipoprotein receptors, lipoprotein lipase activity and intracellular lipase activity are present in placental tissues. The lipids are taken up, catabolised, re-esterified and stored transiently within the placenta, until being re-catabolised for further free fatty acid release into the fetal circulation (6).

The regulatory pathways that control placental lipid metabolism are poorly understood, and we hypothesised that peroxisome proliferator activated receptors (PPARs) may be important regulators of placental lipid homeostasis.

PPARs are members of the nuclear hormone receptor superfamily of ligand-dependent transcription factors, deeply involved in adipocyte differentiation and lipid homeostasis (7). The three identified subtypes, named PPARα, PPARγ and PPARδ, interact with specific DNA response elements within promoter regions of target genes as complexes with the 9-cis-retinoic acid receptor (RXR). When activated by agonist-ligand binding, the heterodimer complex recruits transcription co-activators and regulates the transcription of genes involved in lipid and carbohydrate metabolism, inflammatory responses and developmental processes (8).

The PPAR subtypes have several endogenous agonists such as prostaglandins, leukotrienes and polyunsaturated fatty acids. On the other hand, both thiazolidinediones and fibrates are pharmacological PPAR ligands utilised in the treatment of obesity, dyslipemias and diabetes (9).

The three PPAR isotypes have been localised in placental cells. Moreover, PPARγ and PPARδ are essential genes for placental development, and their inactivation induces profound anomalies in the vasculature and structure of the labyrinth zone that leads to fetal death by midgestation (10,11). In the present work we utilised control and diabetic rats as an experimental approach to study placental lipid metabolism at midgestation in both healthy and diabetic pregnancies. The diabetic model employed was obtained through neonatal streptozotocin administration, and constitutes a mild diabetic model previously characterised by our group (12), in which glycemia levels (150-230 mg/dl) are similar to those frequently found in diabetic women during pregnancy. The objective of the present study was therefore to address a putative role of PPARs activators as regulators of placental lipid levels, synthesis and catabolism in placental tissues obtained from control and diabetic rats at mid-gestation.

Materials and Methods

Animals and placental preparations

Albino Wistar rats were bred in the laboratory with free access to Purina rat chow and water, in a lighting cycle of 14 h light: 10 h dark. At 2 days of age, they were injected with either streptozotocin (90 mg/kg s.c.) (Sigma, St Louis, MO, USA) in citrate buffer (0.05 M, pH 4.5) or buffer alone (controls). Four days after birth, neonates exhibiting glycosuria higher than 500 mg/dl were considered diabetic. The spontaneous evolution of this treatment leads to a diabetic state as previously described (13). Adult diabetic rats presented glycemia levels higher than 150 mg/dl and a marked glucose intolerance, while control rats showed glycemia levels below 110 mg/dl. In the evening of proestrus, control and diabetic females, weighing between 200-300 g were caged overnight with control males. The following day was designated as day 0.5 of gestation if sperm cells were found in the vaginal smear. A total of 50 animals were employed and 85% of them conceived when mated in proestrous. The resorption rate was 2% in control animals and 10% in diabetic animals. Animals were killed by cervical dislocation on day 13.5 of gestation, and their placentas were removed and placed in Petri dishes containing Krebs-Ringer-Bicarbonate (KRB) solution. In this work, we utilized short term placental explant cultures to define PPAR agonist placental effects. As PPARs may influence maternal metabolism different *in vivo* effects can not be discarded. Placental explants from eight diabetic and eight control animals were cultured for three hours in a metabolic shaker at 37°C, either with or without PPARs agonists: clofibrate (20 μM); 15-deoxy$\delta^{12,14}$ prostaglandin J_2 (15dPGJ_2, 2 μM); or carbaprostacyclin (cPGI_2, 1 μM) (Cayman Chemical Co, MI, USA). After incubation, tissues were frozen at –70°C for further determination of lipid levels and the incubating medium was preserved at –20°C for further determination of lipid catabolism as described below. The guidelines

for the care and use of animals approved by our Institution were followed, according to the ILAR guide for the Care and Use of Laboratory Animals (1996), http://www.nih.gov/sigs/bioethics/animals.html.

Determination of lipid levels

Total lipids were extracted in methanol: chloroform (2:1, v/v) and then concentrated in a Savant Speed-Vac concentrator. Triglycerides, cholesterol, cholesteryl esters and phospholipids were quantified by thin layer chromatography (TLC), stained with iodine vapour and analysed using image analysis SIGMAGEL (Sigma, MO, USA) as reported previously (14). The placental lipids were chromatographed with a solvent system consisting of hexane:ethyl ether:acetic acid (80:20:2, v/v). After development, the TLC plate was dried for 5 min in the dark under a N_2 stream and lipids were stained with iodine vapour. Lipid species were quantified by comparison with known amounts of pure lipid standards run on the same plate. Results are expressed as µg/mg protein and statistically analysed by analysis of variance.

Determination of lipid synthesis

The *de novo* synthesis of labelled lipids from ^{14}C-acetate was evaluated as reported previously (14). The placental explants from another eight diabetic and eight control animals were cultured as described above, with the addition of 37 MBq/l [$^{1,2\text{-}14}$C]-acetate (1.96 GBq/mmol) to the incubation medium. After incubation, tissues were washed three times to remove adherent ^{14}C-acetate and were then stored at -70°C until lipid extraction. The extraction and separation of lipids by TLC were performed as described above. All samples were chromatographed in parallel with pure lipid standards. Radioactive spots corresponding to the different ^{14}C-labelled lipid species were scraped into vials and counted in a liquid scintillation counter. Results are expressed as dpm/µg protein and statistically analysed by analysis of variance.

Determination of lipid catabolism

Glycerol release into the culture medium generated during the hydrolysis of triglycerides and phospholipids in the tissues was determined enzymatically, as reported previously (15,16). Briefly, 0.2 ml of placental explant incubation medium was allowed to react with 1 ml of assay solution containing glycine (15 mg/ml), $MgCl_2$ (0.4 mg/ml), ATP (0.75 mg/ml), NAD^+ (0.36 mg/ml), hydrazine hydrate 20% (v/v) (Sigma, MO, USA), glycerokinase (0.42 units/ml) and glycerol-3-phosphate dehydrogenase (2.5 units/ml) (Roche, IN, USA). After 45 min, OD was read at 340 nm in a microtitre plate using glycerol as the standard. Results are expressed as nmol/mg protein and statistically analysed by analysis of variance.

Results

In order to investigate whether PPAR ligands regulate lipid metabolism at midgestation, both control and diabetic rat placental explants were incubated for 3 h in KRB medium in the presence or absence of PPARs agonists, followed by determination of phospholipid, triglyceride, cholesterol and

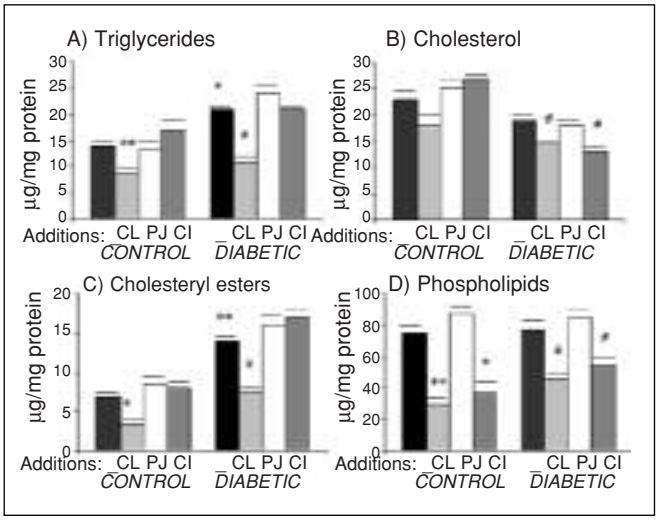

Figure 1. Effect of PPARs agonists on (A) triglyceride, (B) cholesterol, (C) cholesteryl esters and (D) phospholipid concentrations in placental explants from control and diabetic rats. Tissues were incubated for 3 h in KRB solution either with or without 20 µM clofibrate (CL), 2 µM 15dPGJ$_2$ (PJ) or 1 µM cPGI$_2$, (CI). Data are the mean ± s.e.m, n=8 in each experimental group. *p<0.05, **p<0.01 compared with control without additions, # p<0.05, compared with diabetic without additions.

cholesteryl ester levels. In the placenta from control rats, we found that the PPARα activator clofibrate (20 µM) diminished triglyceride (43%, p<0.01), phospholipids (63%, p<0.01) and cholesteryl esters levels (46%, p<0.05), and did not modify cholesterol levels (Figure 1). Differently, PPARγ agonist 15dPGJ$_2$ (2 µM) did not modify any of the lipid species analysed. On the other hand, the PPARδ activator cPGI$_2$ (1 µM) reduced phospholipid levels (51%, p<0.05) and did not modify any of the other lipid species analysed (Figure 1). In the placenta from diabetic rats, which show increased triglyceride (50%, p<0.05) and cholesteryl ester levels (93%, p<0.01), the effects of PPARs agonists on lipid levels were studied and found similar to those detected in the healthy group. Indeed, the PPARα activator clofibrate (20 µM) reduced triglyceride (48%, p<0.02), phospholipid (41%, p<0.05), cholesterol (24%, p<0.05) and cholesteryl ester levels (44%, p<0.02) in the placenta from diabetic animals. The PPARγ ligand 15dPGJ$_2$ (2 µM) did not modify the levels of the studied lipids. Also, the PPARδ agonist cPGI$_2$ reduced phospholipid (30%, p<0.05) and cholesterol levels (35%, p<0.05), and did not change triglyceride and cholesteryl ester levels in the placenta from diabetic rats (Figure 1).

In order to further analyse lipid metabolic pathways, we studied the effects of PPARs agonists on the *de novo* lipid synthesis by incubating placental explants for 3 h in KRB medium containing radiolabelled acetate added with or without the PPARs ligands. In the placenta from control rats, we found that the addition of PPARs activators reduced the *de novo* synthesis of different lipid species. Indeed, clo-fibrate (20 µM) reduced the synthesis of all lipid species analysed (triglycerides 35%, p<0.05; phospholipids 43%, p<0.05; cholesterol 63%, p<0.02

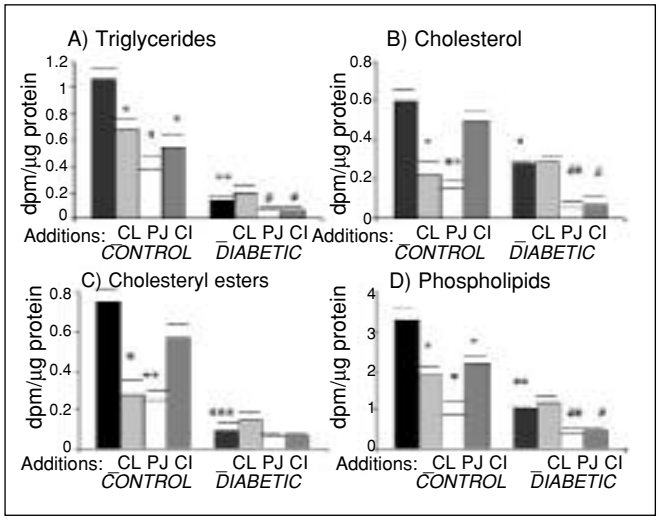

Figure 2. Effect of PPARs agonists on the *de novo* synthesis of (A) triglyceride, (B) cholesterol, (C) cholesteryl esters and (D) phospholipid concentrations in placental explants from control and diabetic rats. Tissues were incubated for 3 h in KRB solution in the presence of [1,2-14C]-acetate (1.96 GBq/mmol) either with or without 20 µM clofibrate (CL), 2 µM 15dPGJ$_2$ (PJ) or 1 µM cPGI$_2$, (CI). Data are the mean ± s.e.m, n=8 in each experimental group. *p<0.05, **p<0.01, ***p<0.001 compared with control without additions, #P<0.05, ## p<0.01 compared with diabetic without additions.

and cholesteryl esters 63%, p<0.02) (Figure 2). Also, 15dPGJ$_2$ (2 µM) diminished the *de novo* synthesis of all the studied lipids (triglycerides 57%, p<0.05; phospholipids 75%, p<0.05; cholesterol 74%, p<0.01 and cholesteryl esters 65%, p<0.01) (Figure 2). In addition, cPGI$_2$ (1 µM) reduced the *de novo* synthesis of triglycerides (40%, p<0.05) and phospholipids (39%, p<0.05), without any changes in the synthesis of cholesterol and cholesteryl esters. In the placenta from diabetic rats, which shows a reduction in the *de novo* synthesis of all lipid species analysed (triglycerides 84%, p<0.01; phospholipids 71%, p<0.05; cholesterol 54%, p<0.05; and cholesteryl esters 87%, p<0.001), we found that the PPARα agonist was devoid of effect. Differently, PPARγ agonist 15dPGJ$_2$ (2 µM) diminished the *de novo* synthesis of triglycerides (58%, p<0.05), phospholipids (58%, p<0.01) and cholesterol (80%, p<0.01), whereas the PPARδ activator cPGI$_2$ (1 µM) also diminished triglycerides (58%, p<0.05), phospholipids (51%, p<0.05) and cholesterol (74%, p<0.05) *de novo* synthesis, without changing the synthesis of cholesteryl esters (Figure 2).

To further evaluate whether PPARs activation regulates the catabolism of esterified lipids in the placenta, placental explants were incubated for 3 h in KRB medium either with or without PPARs ligands and then glycerol levels released into the incubation medium were assessed. In the placenta from healthy animals we found that the PPARα agonist clofibrate (20 µM) significantly enhanced placental lipid catabolism (133%, p<0.01) (Figure 3). No modification on glycerol release was detected in the presence of the PPARγ agonist 15dPGJ$_2$ (2 µM). Interestingly, an important increase in glycerol release was found in the presence of the PPARδ agonist cPGI$_2$ (1 µM, 224%, p<0.001) (Figure 3). In the diabetic group, in which a significant increase in placental lipid catabolism was found (99%, p<0.001), we observed that both the PPARα and PPARγ agonists employed did not modify glycerol release. Differently, the PPARδ agonist cPGI$_2$ (1 µM) stimulated lipid catabolism, as indicated by the enhanced release of glycerol (53%, p<0.01) to the incubation medium (Figure 3).

Discussion

The results of this work reveal that the three PPARs isotypes are indeed involved in the regulation of the placental lipid metabolism. The placenta is an active regulator of the accretion and transfer of lipids to the fetal circulation, and therefore a functional regulator of the quality and quantity of lipids that have access to the developing fetus (4).

The impact of maternal diabetes in the placental lipid metabolism may be the result of the profound alterations in the lipid profile induced by this pathology in both humans and experimental diabetic models (4,17). In addition, the placental derangements resulting from the increased pro-inflammatory agents and oxidative stress in the diabetic placenta, partially originated in an anomalous lipid profile, may lead to abnormalities that impair placental development, function and metabolism (18).

As previously, in this work, too, we found that even under moderate hyperglycemia, placental lipid metabolism is profoundly affected (14). Indeed, we found increased lipid levels and catabolism in the placenta from diabetic rats at midgestation, thus suggesting an increase in lipid turnover.

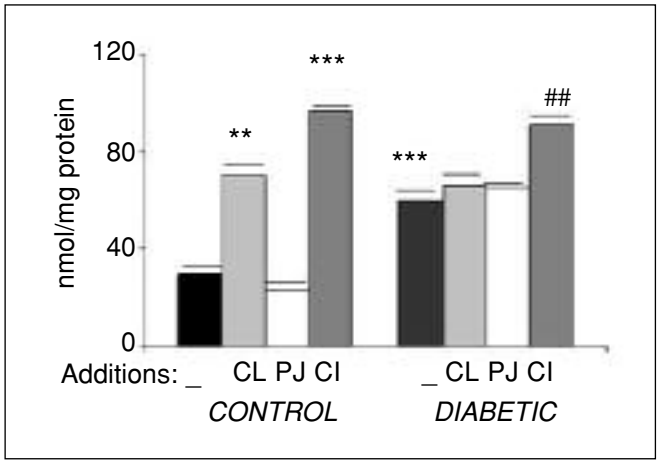

Figure 3. Effect of PPARs agonists on glycerol released into the incubation medium by placental explants from control and diabetic rats. Tissues were incubated for 3 h in KRB solution either with or without 20 µM clofibrate (CL), 2 µM 15dPGJ$_2$ (PJ) or 1 µM cPGI$_2$, (CI). Data are the mean ± s.e.m, n=8 in each experimental group. **P<0.01, ***P<0.001 compared with control without additions, ##P<0.01 compared with diabetic without additions.

On the other hand, the *de novo* lipid synthesis is reduced in this diabetic tissue, probably a mechanism that compensates the increased lipid fluxes reaching the placenta from maternal circulation. Both the increased catabolism and the reduced *de novo* lipid synthesis suggest active pathways to limit over-accumulation of placental lipids, in which PPARs appear to be involved (14).

PPARs have been found to be elevated in trophoblastic cells at midgestation (8). PPARγ, the best characterized isotype in the placenta, is involved in trophoblast differentiation and invasive behaviour (19). In the present work, we demonstrated that each PPAR isotype activates particular and relevant regulatory pathways in the placenta. In this tissue, PPARα leads to a reduction in lipid levels, probably the result of a clear catabolic effect, and also to a reduction in the *de novo* lipid synthesis. Indeed, the potent catabolic effects of PPARα are well established in different tissues (20). Alterations in the PPARα metabolic functions in the diabetic placenta may arise from altered levels of these nuclear receptors, as previously found for other PPAR isotypes (21), and will require clarification through further research.

On the other hand, PPARγ, an essential receptor for placental development, is clearly involved in adipocyte differentiation and function (10). In this work we found that PPARγ activators did not modify placental lipid levels and catabolism, but reduced the *de novo* lipid synthesis in both control and diabetic placenta. Studies performed in cultured trophoblasts show an increased uptake of fatty acids in response to PPARγ activation (22). Therefore, the reduction of the *de novo* lipid synthesis observed in our studies may be a compensatory response to an increase in the fatty acids up-taken by the trophoblastic cells.

Finally, the activation of PPARδ, another essential gene for placental development, leads to catabolic effects in adipose tissues and other cell types (11,23). We found that the PPARδ agonist reduced phospholipid levels, probably as a result of both an important stimulation of the catabolism of these lipids and a reduction in the *de novo* lipid synthesis.

In conclusion, our data demonstrate that PPARs agonists are important regulators of the placental lipid metabolism and that the activation of each PPAR isotype leads to specific effects, clearly related to different lipid metabolic pathways. Due to the profound imbalance in lipid metabolism in the placenta from diabetic gestations, and the possibility to activate placental PPARs through both pharmacological and endogenous ligands, our results reveal novel signalling pathways that may lead to new therapeutic strategies in the regulation of lipid availability to the developing fetus in diabetic gestations.

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