High-fat diet-induced reduction in nitric oxide-dependent arteriolar dilation in rats: role of xanthine oxidase-derived superoxide anion

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Tiron or xanthine oxidase inhibitor allopurinol enhanced ACh (maximum: 90\% and 93\%) produced by 10.220.32.246 on September 9, 2017 http://ajpheart.physiology.org/ Downloaded from

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THE METABOLIC SYNDROME is commonly defined as a group of risk factors or abnormalities closely associated with obesity and insulin resistance that markedly increase the risk for both cardiovascular disease and diabetes mellitus. Population-based studies suggest that obesity is the driving force behind the high prevalence of metabolic syndrome (38). In the past decade, the prevalence of obesity increased dramatically (17) in association with a continuous rise of cardiovascular diseases, such as hypertension (15). Despite the intensive investigations, the mechanisms by which obesity promotes cardiovascular diseases are not completely revealed.

It seems well established that diabetes mellitus and hypertension are associated with disturbed microcirculation, and it is believed that the key event developing early on is endothelial dysfunction (9 –11, 18, 36). Previous studies revealed that, under these pathological circumstances, one of the characteristic features of endothelial dysfunction is the impaired endothelium-dependent dilation, in part, because of a reduction in the bioavailability of the signaling molecule nitric oxide (NO; see Refs. 16, 24, and 37). The endothelial production of NO depends on the delicate balance between NO production via endothelial NO synthase and inactivation by reactive oxygen species (ROS), such as superoxide anion. Increased ROS generation is an important aspect of microvascular dysfunction, and an enhanced production of ROS interferes with several endothelial mechanisms, such as NO mediation, leading to impaired endothelium-dependent arteriolar dilations (9, 18, 24). In this context, previously we have demonstrated a key role for an excess vascular production of superoxide anion, which reduces flow- and agonist-induced dilation of coronary arterioles by interacting with endothelium-derived NO in a mouse model of Type 2 diabetes mellitus (leptin gene receptor-deficient db/db mice; see Refs. 3 and 4). Also, in skeletal muscle arterioles, Frisbee and Stepp (18) have found that, in Type 2 diabetic and hypertensive obese Zucker rats (with similar mutation in leptin gene receptor), NO mediation of arteriolar dilations is impaired because of increased superoxide production. These studies suggested that, in these obese models of Type 2 diabetes mellitus, hyperglycemia and hypertension are primarily responsible for the development of microvascular dysfunction.

Clinical observations suggested that obesity, in particular the visceral form, is associated with the early development of endothelial dysfunction (1), although the exact mechanisms are not completely understood (10). In recent observations, great attention has been devoted to the high-fat content of diet, which leads to obesity and consequent vascular dysfunction, even before the development of Type 2 diabetes mellitus. During the course of these studies, a primary role for high-fat consumption leading to endothelial dysfunction has been proposed (14, 32). Studies were initiated in animal models of human obesity aiming to elucidate the adverse effects of high-fat diet (HFD) on vascular reactivity (20, 28, 34, 35, 44).
These studies revealed that high-fat consumption is associated with impaired endothelium-dependent dilations of large conduit vessels, and a key role for altered NO signaling mechanisms was proposed (28, 35).

It is well known that circulatory resistance and tissue perfusion is determined primarily by small arteries and arterioles. However, few if any studies have investigated the effect of HFD-induced obesity on the potential alterations of microvascular function. Thus, in the present study in rats fed with HFD, we aimed to characterize the arteriolar dysfunction and reveal some of the underlying mechanisms. We have used isolated skeletal muscle arterioles to exclude neural and hormonal vasoregulatory mechanisms that may also be affected by HFD (5, 7).

METHODS

Experimental animals. Male Wistar rats were purchased from Charles River Laboratories. Rats were maintained in the animal care facility at the university with a 12:12-h light-dark cycle and were given free access to food and water. All protocols were approved by the Institutional Animal Care and Use Committee at the University of Debrecen in accordance with the Hungarian Animal Protection Law. Rats were maintained on standard rat chow or on a HFD (EU modified rodent diet with 60% fat, 58Y1, TestDiet; PMI Nutrition International) for 10 wk. The body weight of the rats was measured every week. After overnight fasting, the rats were anesthetized with an intraperitoneal injection of pentobarbital sodium (50 mg/kg). The left common carotid artery was cannulated for continuous monitoring of blood pressure with a physiological pressure transducer. Blood samples were collected from the carotid artery, centrifuged, and kept frozen at −80°C until chemical assays. Under anesthesia, the gracilis muscle was removed, and the animals were then killed by an additional injection of pentobarbital sodium (150 mg/kg), and the carotid arteries were dissected. The inguinal and retroperitoneal fat pads were excised and weighed.

Analytical procedures. The plasma level of total cholesterol and glucose was measured by colorimetric enzymatic assays (Cobas Integra automated analyzer; Roche). Insulin was measured using an RIA-based commercially available assay (BYK Sangtec). Isolation of gracilis muscle arterioles. With the use of surgical instruments and an operating microscope, the gracilis arteriole (~1.5 mm in length) was isolated and transferred to organ chambers containing two glass micropipettes filled with physiological salt solution (PSS) composed of (in mmol/l) the following: 110.0 NaCl, 5.0 KCl, 2.5 CaCl₂, 1.0 MgSO₄, 1.0 KH₂PO₄, 5.5 glucose, and 24.0 NaHCO₃, equilibrated with a gas mixture of 10% O₂-5% CO₂-balance nitrogen, at pH 7.4. The vessel was cannulated at both ends, and the micropipettes were connected with silicone tubing to a pressure servo control system (Living Systems Instrumentation) to set the intraluminal pressure to 80 mmHg. The temperature was set at 37°C by a circulating bath temperature controller (Cole Parmer). Images of the sections were collected with a digital camera (CFW 1310; CFW, Inc) and background-corrected values were normalized to tissue weight. Scintillation counts were also obtained after the addition of allopurinol (100 µmol/l, for 30 min) or apocynin (100 µmol/l, for 30 min). In separate protocols, after control signals were obtained, carotid arteries were incubated for an additional 30 min in the presence of 100 µmol/l NADH or 100 µmol/l xanthine, allowing an estimation of the stimulated amount of superoxide produced by the NAD(P)H oxidase or xanthine oxidase (27).

Immunohistochemistry. A piece of gracilis muscle including the gracilis arteriole from control (n = 4) and HFD rats (n = 4) were embedded and frozen in optimum-cutting temperature compound (Tissue Tek; Electron Microscopy Sciences). Acetone-fixed consecutive sections (10 µm thick) were immunolabeled with a monoclonal antibody against xanthine oxidase (dilution 1:50; LabVision). Immunostaining was visualized by using an avidin-biotin horseradish peroxidase visualization system (Vectastain kit; Vector Laboratories), stained with diaminobenzidine tetrahydrochloride. For nonspecific binding, the primary antibody was omitted on consecutive sections. Images of the sections were collected with a digital camera (CFW 1310; Scion) connected to a Nikon Eclipse 80 microscope.

Data analysis. Data are expressed as means ± SE. Agonist-induced arteriolar responses were expressed as changes in arteriolar diameter as a percentage of the maximum dilation defined as the passive diameter of the vessel at 80-mmHg intraluminal pressure in a Ca²⁺ free medium. Statistical analyses were performed by two-way repeated-measures ANOVA followed by Tukey’s post hoc test or Student’s t-test as appropriate. P < 0.05 was considered statistically significant.

RESULTS

Within 2 wk of commencing the HFD, the body weights of rats became significantly greater than those of controls fed the standard diet, and the weight difference further increased up to 10 wk of HFD feeding (Fig. 1). The average food intake was less in the HFD group than in the normal diet group (623 and 153 g animal⁻¹·wk⁻¹, respectively), whereas the calculated average calorie intake was similar in the two groups (623 and 613 cal·animal⁻¹·wk⁻¹, respectively). The weight gain was accompanied by a significantly greater inguinal and retroperitoneal fat pad mass (Table 1). Serum glucose, insulin, and total cholesterol levels were significantly elevated in HFD rats compared with controls. In addition, confirming previous findings (5, 7), the arterial blood pressure was significantly increased in anesthetized HFD rats (Table 1).

Agonist-induced arteriolar responses. In gracilis muscle arterioles isolated from control and HFD rats, there were no significant differences between the active (158 ± 9 and 177 ± 10 µm, respectively) and passive (in Ca²⁺-free PSS, 233 ± 9

min), an inhibitor of the endothelial NO synthase. In separate experiments, arterioles of control and HFD rats were also incubated in the presence of superoxide scavenger Tiron (1 µmol/l, for 30 min; see Ref. 27), and arteriolar responses were obtained again. In another protocol, the same ACh- and histamine-induced arteriolar responses were tested after incubation with allopurinol (100 µmol/l, for 30 min), a xanthine oxidase inhibitor, or apocynin (100 µmol/l, for 30 min), an NAD(P)H oxidase inhibitor (2, 4).

Quantification of vascular superoxide production by lucigenin-enhanced chemiluminescence assay. Vascular superoxide production was assessed in carotid arteries isolated from control and HFD rats by the lucigenin-enhanced chemiluminescence method according to a modified protocol of Mohazzab et al. (27). A segment of the carotid artery was removed from rats, cleared of connective tissue, immersed in PSS (37°C), and incubated for 60 min. The arteries were then placed in scintillation vials containing HEPES-buffered (10 mmol/l, pH 7.4) PSS and lucigenin (10 µmol/l). Chemiluminescence was measured in a liquid scintillation counter (Tri-Carb 2800TR). From the lucigenin-enhanced chemiluminescence assay, enhanced chemiluminescence was determined as the difference in scintillation counts before and after the addition of lucigenin (10 µmol/l, for 30 min). The lucigenin-enhanced chemiluminescence was used to estimate the stimulated amount of superoxide produced by the NAD(P)H oxidase or xanthine oxidase (27).

H2108 HIGH-FAT DIET REDUCES ARTERIOULAR DILATION

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and 242 ± 10 μm, respectively) diameters at 80 mmHg intraluminal pressure.

In arterioles of HFD rats, dilations in response to cumulative doses of ACh and histamine were significantly decreased compared with those of control vessels (Fig. 2). Arteriolar responses to the NO donor SNP were not different between vessels of control and HFD rats (Fig. 2). Inhibition of NO synthesis by L-NAME decreased ACh- and histamine-induced dilations in control arterioles, whereas it had no effect on ACh- and histamine-induced responses in arterioles of HFD rats (Fig. 3).

To provide evidence for the role for enhanced superoxide production, the cell-permeable superoxide dismutase (SOD) mimetic Tiron was administered extraluminally, a method that was shown to effectively scavenge superoxide (27). Administration of Tiron significantly enhanced histamine-induced dilation in arterioles isolated from HFD rats but did not affect ACh-evoked responses in HFD or agonist-induced dilations in control vessels (Fig. 4).

To reveal the possible source of superoxide, the same arteriolar responses were assessed after incubation of arterioles with the NAD(P)H oxidase inhibitor apocynin or the xanthine oxidase inhibitor allopurinol (2, 4). In arterioles of control rats,

### Table 1. Basic characteristic of rats after 10 wk of normal diet (control) and high-fat diet

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 9)</th>
<th>HFD (n = 9)</th>
</tr>
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<tbody>
<tr>
<td>Body wt, g</td>
<td>378±12</td>
<td>504±23*</td>
</tr>
<tr>
<td>Inguinal fat pad wt, g</td>
<td>2.4±0.4</td>
<td>6.4±0.9*</td>
</tr>
<tr>
<td>Retropertioneal fat pad wt, g</td>
<td>4.8±0.5</td>
<td>22.7±2.6*</td>
</tr>
<tr>
<td>Serum glucose, mmol/l</td>
<td>7.0±0.2</td>
<td>9.9±0.9*</td>
</tr>
<tr>
<td>Serum insulin, pmol/l</td>
<td>96±9</td>
<td>244±15*</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/l</td>
<td>1.10±0.09</td>
<td>1.72±0.09*</td>
</tr>
<tr>
<td>Mean arterial blood pressure, mmHg</td>
<td>101±2</td>
<td>111±5*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. HFD, high-fat diet. *Significant differences (P < 0.05).
neither apocynin nor allopurinol affected agonist-induced dilations. On the other hand, in arterioles of HFD rats, allopurinol, but not apocynin, significantly enhanced ACh- and histamine-induced dilation (Fig. 5).

Quantification of superoxide production by lucigenin-enhanced chemiluminescence. Vascular superoxide production was assessed in carotid arteries of control and HFD rats by the lucigenin-enhanced chemiluminescence method (27). Summarized data show that there was an enhanced lucigenin chemiluminescence in carotid arteries of HFD rats that was inhibited by preincubation with SOD mimetic Tiron (Fig. 6). Vascular superoxide production was also assessed in the presence of apocynin or allopurinol. Apocynin did not affect superoxide production either in control [from 463 ± 98 to 479 ± 122 counts·min⁻¹·cpm⁻¹·mg⁻¹] or HFD (from 1,152 ± 248 to 1,002 ± 256 cpm/mg) vessels. Allopurinol had no effect in control vessels (from 410 ± 20 to 469 ± 109 cpm/mg), whereas it significantly reduced superoxide production in carotid arteries of HFD rats (from 1,055 ± 106 to 600 ± 258 cpm/mg, P < 0.05).

Also, lucigenin-enhanced chemiluminescence assay was performed in the presence of NADH or xanthine to measure the NAD(P)H oxidase- and xanthine oxidase-derived superoxide production, thereby assessing the enzyme activity of the NAD(P)H oxidase and xanthine oxidase in the vessels. In the presence of NADH, there was no significant difference in the stimulated superoxide production between the two groups of vessels, whereas the presence of xanthine resulted in a significantly enhanced superoxide production in carotid arteries from HFD rats compared with control vessels (Fig. 6).

Immunostaining for xanthine oxidase. Compared with control arterioles, an enhanced xanthine oxidase immunostaining was detected in the gracilis arterioles of HFD rats, which was mainly localized in the endothelial layer of arterioles (Fig. 6).

DISCUSSION

The salient finding of this study is that high fat diet in rats impairs NO mediation of endothelium-dependent dilations of skeletal muscle arterioles, primarily because of an increased xanthine oxidase-derived superoxide anion production. These findings suggest that HFD promotes the development of oxidative stress and endothelial dysfunction in arterioles. Obesity has been found to increase the incidence of cardiovascular diseases (34). High fat containing Western diet-associated obesity can lead to insulin resistance, hyperinsulinemia, and hypercholesterolemia that have been proposed to be involved in the development of endothelial dysfunction (1, 9, 10, 31), although the underlying mechanisms are not completely understood. Previous clinical observations revealed that even a single high-fat meal can lead to a transient endothelial dysfunction, measured as reduced occlusion-induced brachial ar-

Fig. 3. Changes in diameter of gracilis arterioles isolated from control (n = 9) and HFD (n = 5) rats in response to cumulative doses of ACh (A and B) and histamine (C and D), before and after incubation with N⋅-nitro-L-arginine methyl ester (l-NAME). Data are means ± SE. *Significant differences (P < 0.05).
tery relaxation in healthy subjects (14, 32). These clinical observations proposed a key role for dietary high-fat content in the development of endothelial dysfunction in obesity.

Thus, animal studies have been initiated to explore the underlying mechanisms by which long-term HFD may promote endothelial dysfunction. These studies demonstrated that high-fat feeding in animals impairs endothelium-dependent relaxation of the large conductance arteries. For instance, it has been found that, in pigs fed with HFD, relaxations to ACh and bradykinin were reduced both in coronary and brachial arteries (20, 44). Also, in rats fed with HFD for 7 mo (34) or for 8 wk (30), relaxation of the aortic rings to ACh was impaired. Mice on HFD for 9 wk also exhibited reduced femoral artery relaxation to the endothelium-dependent dilator ACh (28). The key role for high-fat feeding was further substantiated by the findings of Reil et al. (33) showing that, in rats, HFD-evoked impairment of aortic ring relaxation was reversed to control levels when the diet was switched off. Collectively, these studies have proposed a pathological role for high-fat content of the diet in the development of endothelial dysfunction in large conductance arteries. However, previously less attention was devoted on the function of microvessels in HFD-induced obesity. Because resistance arteries are of physiological importance in the control of circulatory resistance and organ perfusion and findings obtained in large arteries cannot be generalized, it seemed necessary to study the impact of HFD specifically on microvessels.

Thus, in this study, we investigated agonist-induced arteriolar dilations in a rat model of HFD-induced obesity. Obesity was induced by HFD composed of 60% of saturated fat. In previous genetic models of Type 2 diabetes and obesity, such as in obese Zucker rats and db/db mice, animals have a nonfunctional leptin receptor, providing a valuable animal model for examining the effect of “overfeeding”-induced Type 2 diabetes. Because of the extreme amount of food consumption and high caloric intake, they become obese, severely hyperinsulinemic, and hyperglycemic. By contrast, in the present study, obesity was induced by high-fat consumption. Thus this model of diet-induced obesity is likely to be the result of the high-fat content of diet rather than the extremely increased caloric intake. After 10 wk of HFD, body weight was significantly elevated, and this weight gain was accompanied by inguinal and retroperitoneal fat pad mass, although the calorie intake was similar in the two groups. HFD for 10 wk was associated with elevated serum insulin, glucose, and total cholesterol levels (Table 1), as reported previously (28, 30). Although the glucose level was slightly, but significantly, elevated in HFD rats compared with controls (Table 1), in other animal models of type 2 diabetes, such as db/db mice (3) or obese Zucker rats (18), animals have about four times higher fasting glucose levels. Thus findings of the present study are likely related primarily to the adverse effect of high-fat content of the diet and consequent hyperinsulinemia, lipid abnormalities on the endothelial regulation of arteriolar tone. In this
study, we have also found that HFD rats exhibited higher mean arterial blood pressure, confirming previous studies that also demonstrated elevation in blood pressure in rats on HFD (5, 41). It is of note that blood pressure regulation in obesity can be influenced by several mechanisms, such as neural (5), hormonal (7), and other mechanisms, including alterations in the intrinsic vasoregulatory function of the resistance arteries (24).

Agonists-induced responses of arterioles after HFD. In the present study, we investigated isolated skeletal muscle arterioles to exclude neural and hormonal mechanisms that may also be affected in diet-induced obesity (5, 7). Gracilis muscle arterioles isolated from HFD rats did not show significant changes in the active and passive (in Ca²⁺/free solution) arteriolar diameters at intraluminal pressure of 80 mmHg compared with control vessels. In arterioles of HFD rats, endothelium-dependent dilations to ACh and histamine were significantly reduced compared with those of control responses, whereas dilations to the NO donor SNP were not different between the two groups (Fig. 2). These findings indicated selective impairment of endothelium-dependent dilations in skeletal muscle arterioles of HFD rats, which is likely to be related to an alteration in subcellular mechanisms rather than specific receptor-mediated signaling. Indeed, previous studies proposed that, in diet-induced obesity, reduced endothelium-dependent dilation is primarily the result of reduced bioavailability of the second messenger NO (28, 34). To test this hypothesis, agonist-induced arteriolar dilations were observed after the inhibition of NO synthesis. The NO synthase inhibitor L-NAME significantly reduced ACh- and histamine-induced dilations in control arterioles; however, it had no effect on responses of HFD vessels (Fig. 3), suggesting a lack of NO mediation of agonist-induced dilations in arterioles of HFD rats.

Demonstration of vascular oxidative stress in HFD. It has been previously reported that HFD was associated with a reduction of endothelial NO synthase protein levels in rat aorta, which was proposed to be responsible for the reduced NO synthesis in this condition (34). Other studies suggested that increased ROS generation is the primary cause of the NO...
inactivation in diet-induced obesity (30, 35). The results of this study support the latter hypothesis because, in skeletal muscle arterioles of HFD rats, the SOD mimetic Tiron significantly enhanced histamine-induced dilations, suggesting a role for increased superoxide production interfering with NO signaling (Fig. 4). It should be noted that the effect of Tiron was less pronounced in ACh-induced responses of HFD arterioles, which is likely due to the smaller role of NO in mediation of this response (24) and depends on primarily non-NO, most likely endothelium-derived hyperpolarizing factor (EDHF)-mediated mechanisms (8). In this context, previous studies suggested that EDHF is less sensitive to ROS (23), and thus dilations mediated by EDHF can persist during oxidative stress. Indeed, in a recent study by Wolfe and de Wit (42), it has been found that apolipoprotein E and low-density lipoprotein receptor-deficient mice fed either with normal or high-cholesterol diet exhibited preserved endothelium-dependent dilation to ACh in the cremaster muscle arteriole in which ACh-dependent dilation is mediated primarily by EDHF.

To further substantiate the primary role for ROS, superoxide production was measured in carotid arteries by the lucigenin-enhanced chemiluminescence method. These studies revealed an increased superoxide anion production in the carotid artery of HFD rats compared with those vessels obtained from control animals (Fig. 6). Although the carotid artery is a conduit blood vessel and findings obtained in carotid arteries cannot be directly extrapolated to microvessels, together with the functional results obtained in isolated arterioles, we propose that in HFD rats vascular superoxide anion production is increased. Previously, it has been shown that, in conditions when the level

![Graph A](image)

![Graph B](image)

![Graph C](image)
of superoxide increases, the bioavailability of NO decreases (11). Thus we propose that in HFD rats, because of the increased level of superoxide, the NO-mediated dilations became reduced in skeletal muscle arterioles.

Source of vascular superoxide in HFD. In the next series of experiments, we aimed to identify the possible source(s) of vascular superoxide production. It has been earlier suggested that excess production of vascular superoxide may be derived from different ROS-producing systems (43), including NAD(P)H oxidase(s) (4, 21), xanthine oxidase (2, 31), uncoupled NO synthase (13, 39), and mithochondrial complexes (29). Previous investigations have proposed a crucial role for the vascular xanthine oxidase and NAD(P)H oxidase(s) in atherosclerosis (31), hyperhomocysteinemia (2), Type 2 diabetes mellitus (4), and hypertension (19); however, the primary source of ROS has not yet been revealed in HFD-induced obesity. In the present study, we have found that the xanthine oxidase inhibitor allopurinol improved agonist-induced dilations in skeletal muscle arterioles and reduced the lucigenin-enhanced chemiluminescence-detected superoxide production in carotid vessels, whereas the NAD(P)H oxidase inhibitor apocynin had no significant affect on these responses (Fig. 5). Correspondingly, an enhanced xanthine oxidase but not NAD(P)H oxidase activity was measured in carotid arteries of HFD rats (Fig. 6). In addition, a marked xanthine oxidase immunostaining was detected in the endothelial layer of HFD, but not in control gracilis arterioles, further substantiating a primary role for xanthine oxidase in mediation of enhanced arteriolar superoxide production (Fig. 6).

Findings of this study are in line with those observations that found enhanced vascular xanthine oxidase activity in animal models of hypercholesterolemia (31, 40). Interestingly, Cardillo et al. (12) have found that, in hypercholesterolemic but not in hypertensive patients, the xanthine oxidase inhibitor oxypurinol improved ACh-induced dilations of the brachial artery. Given that, one can speculate that primary alterations in lipid metabolism could lead to the distinct activation of vascular xanthine oxidase. It is known that xanthine oxidase activation may be a result of several biochemical mechanisms, leading to reversible or irreversible modifications of this enzyme. For instance, elevations of intracellular Ca\(^{2+}\) concentrations, oxidative stress, thiol modification, or nonenzymatic proteolysis have been proposed to be involved in this process (6). Also, it has been found that a circulating form of xanthine oxidase may bind to bovine aortic endothelial cells in culture, leading to a 10-fold increase in specific activity of the enzyme (22), and this mechanism has been proposed to be responsible for the enhanced ROS production in aorta of hypercholesterolemic rabbits (40). Although these aforementioned mechanisms related to abnormal lipid metabolisms likely operate in HFD-induced obesity as well, further investigations are needed to substantiate this idea.

Taken together, this study demonstrates a key role for endothelial xanthine oxidase-derived superoxide production, which is responsible for the reduced NO-mediated dilations of skeletal muscle arterioles of rats fed a HFD. We propose that these alterations in the local regulation of arteriolar resistance may contribute to the development of microvascular dysfunction and hypertension in HFD-induced obesity.

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