Free fatty acids/triglycerides increase ocular and subcutaneous blood flow

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Polak, Kajja, Leopold Schmetterer, Alexandra Luksch, Susanna Gruber, Elzbieta Polska, Vanessa Peternell, Michaela Bayerle-Eder, Michael Wolzt, Michael Krebs, and Michael Roden. Free fatty acids/triglycerides increase ocular and subcutaneous blood flow. Am J Physiol Regulatory Integrative Comp Physiol 280: R56–R61, 2001.—Elevated plasma free fatty acids (FFA) induce skeletal muscle insulin resistance and impair endothelial function. The aim of this study was to characterize the acute hemodynamic effects of FFA in the eye and skin. A triglyceride (Intralipid 20%, 1.5 ml/min/heparin (bolus: 200 IU; constant infusion rate: 0.2 IU·kg−1·min−1) emulsion or placebo was administered to 10 healthy subjects. Measurements of pulsatile choroidal blood flow with laser interferometry, retinal blood flow with the blue field entoptic technique, peak systolic and end diastolic blood velocity (PSV, EDV) in the ophthalmic artery with Doppler sonography, and subcutaneous blood flow with laser Doppler flowmetry were performed during an euglycemic somatostatin-insulin clamp over 405 min. Plasma FFA/triglyceride elevation induced a rise in pulsatile choroidal blood flow with laser interferometry, retinal blood flow with the blue field entoptic technique, peak systolic and end diastolic blood velocity (PSV, EDV) in the ophthalmic artery with Doppler sonography, and subcutaneous blood flow with laser Doppler flowmetry were performed during an euglycemic somatostatin-insulin clamp over 405 min. Plasma FFA/triglyceride elevation induced a rise in pulsatile choroidal blood flow by 25 ± 3% (P < 0.001) and in retinal blood flow by 60 ± 23% (P = 0.0125). PSV increased by 27 ± 8% (P = 0.001), whereas EDV was not affected. Skin blood flow increased by 149 ± 38% (P = 0.001). Mean blood pressure and pulse rate remained unchanged, whereas pulse pressure amplitude increased by 17 ± 5% (P = 0.019). Infusion of heparin alone had no hemodynamic effect in the eye or skin. In conclusion, FFA/triglyceride elevation increases subcutaneous and ocular blood flow with a more pronounced effect in the retina than in the choroid, which may play a role for early changes of ocular perfusion in the insulin resistance syndrome.

Hyperlipidemia; blood flow; blood pressure; retina; choroidea

A NUMBER OF DISEASES, in particular states of insulin resistance (2, 21), is associated with elevated plasma concentrations of free fatty acids (FFA). Previous studies on the physiological impact of FFA focused on glucose metabolism as well as on blood flow. Short-term FFA/triglyceride elevation has been shown to decrease skeletal muscle glucose transport, phosphorylation, and glycogen synthesis thereby acutely inducing insulin resistance (8, 24). However, conflicting results were reported concerning the hemodynamic effects of FFA in brachial and femoral vessels. Elevation of FFA concentrations from exogenous or endogenous sources increased leg blood flow by 20%, caused dysfunction of endothelial-dependent vasodilation associated with a modest rise in systolic arterial pressure, but had no effect on endothelial-independent vasodilation (30). In contrast, other studies found that transient hypertriglyceridemia/FFA elevation decreases both endothelial-dependent and endothelial-independent dilation of the brachial artery in healthy young men (15).

In humans, the hemodynamic effect of FFA has so far only been investigated locally in large brachial and femoral vessels. Although invasive investigation of other vascular beds in healthy humans is not applicable, the vascular beds of the eye are accessible with optical systems that enable us to monitor real-time hemodynamic effects with noninvasive techniques. The aim of this study was therefore to examine in detail the hemodynamic effects of FFA in the eye, inducing FFA/triglyceride elevation by a systemic triglyceride/heparin infusion. Pulsatile choroidal and retinal blood flow were assessed with laser interferometry and the blue field entoptic technique, respectively. In addition, subcutaneous blood flow was determined employing laser Doppler flowmetry.

RESEARCH DESIGN AND METHODS

Subjects

After approval by the Ethics Committee of Vienna University School of Medicine, 10 healthy male nonsmoking volunteers without family history of diabetes or lipid disorders were studied (age range: 20–32 yr; mean ± SD: 25 ± 3 yr). The nature of the study was explained, and all subjects gave written consent to participate. All volunteers passed a pre-study screening during the 4 wk before the first study day,

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which included medical history, physical examination and routine laboratory tests, 12-lead electrocardiogram (ECG), oral glucose tolerance test, and ophthalmic examination. Inclusion criteria were normal screening examinations and ametropia of <3 diopters.

Experimental Design

The study was performed in a balanced, randomized, placebo-controlled two-way crossover design with a washout period of at least 7 days between the study days. The subjects under study as well as the investigators who assessed ocular, skin, and systemic hemodynamics were masked with regard to the treatment. The investigator who performed the insulin-glucose clamp was unmasked, because blood samples during triglyceride infusion can easily be identified due to lipemia. All studies were performed under conditions of a somatostatin-insulin clamp. Each subject received triglycerides with heparin or placebo (saline) on different study days in a randomized sequence.

Preceding the main study, a pilot study was performed on five healthy subjects, who also participated in the main study. These subjects received intravenous heparin alone to exclude possible hemodynamic actions of heparin per se.

Study Protocol

All studies were started at 0800 in the morning in a quiet room with a constant room temperature of 22°C. On each trial day, two plastic cannulas were inserted into antecubital veins, one for administration of infusions and one for blood sampling. After a 20-min resting period in a sitting position, baseline measurements of ocular hemodynamics, skin blood flow, blood pressure, and pulse rate (PR) were performed.

At time 0, the somatostatin infusion (0.1 µg·kg⁻¹·min⁻¹; UCB Pharma, Vienna, Austria) was started. At +10 min, the euglycemic insulin clamp was implemented (6) for 360 min with infusion of insulin (Huminsulin “Lilly,” Fegersheim, France) at a rate of 0.1 mU·kg⁻¹·min⁻¹ to maintain fasting plasma insulin concentration and of glucose (n-glucose 20%, Leopold Pharma, Linz, Austria) to prevent a fall of plasma glucose. Simultaneously, infusions of triglyceride emulsion (Intralipid 20%, 1.5 ml/min; Pharmacia and Upjohn, Vienna, Austria) with heparin (bolus: 200 IU; constant infusion rate: 0.2 IU·kg⁻¹·min⁻¹; Immuno AG, Vienna, Austria) or placebo (normal saline) were started. To determine plasma glucose concentration, arterialized venous blood samples were drawn every 5 min from the contralateral arm, which was heated in a 40°C blanket. Blood samples were drawn at baseline and after 45, 90, 180, 270, and 360 min and instantaneously frozen to determine plasma concentrations of triglycerides, FFA, and insulin.

Analytic Methods

Glucose concentration was determined by using the glucose oxidase method (Glucose analyzer II, Beckmann Instruments, Fullerton, CA). Plasma concentrations of triglycerides and FFA were measured by using enzymatic methods (Sigma Chemical, St. Louis, MO) and microfluorimetric methods, respectively. Plasma insulin concentrations were determined by using a double-antibody RIA (Diagnostic Systems Laboratories, Webster, TX).

Hemodynamic Measurements

Systemic hemodynamics. Blood pressure was measured in 15-min intervals during the study period. PR and a real-time ECG were monitored continuously. Systolic (SBP), diastolic (DBP), and mean blood pressures were measured from the upper arm by an automated oscillometric device. PR was automatically recorded from a finger-pulse oxymeter (HP-CMS patient monitor, Hewlett Packard, Palo Alto, CA). This system has been previously evaluated (32), and it is regularly checked by manual calibration.

Laser interferometry. Pulse synchronous pulsations of the ocular fundus were measured by a laser interferometric method, described in detail by Schmetterer et al. (27). The ocular fundus of the subject is illuminated by a high-coherence laser beam (λ = 783 nm) along the optical axis. The light is reflected at both the retina and the outer surface of the cornea, the latter serving the reference wave. The relative distance changes between the cornea and retina during a cardiac cycle can be measured by an analysis of the interference fringes, which are generated by the two reemitted waves. The distance between the cornea and retina decreases during systole and increases during diastole in the order of several micrometers. The fundus pulsation amplitude (FPA), which is the maximum distance change between the cornea and retina during the cardiac cycle, has been shown to estimate pulsatile blood flow on the selected fundus location (25). The interferometer is coupled to a fundus camera (PK-30 Zeiss, Oberkochen, Germany), which allows real-time inspection of the measurement point on the retina. This measurement point is ~20 to 50 µm in diameter, therefore high topographic inspection is achieved. Measurements were performed in the fovea to assess pulsatile choroidal blood flow.

Blue field entoptic technique. Retinal microcirculation was assessed with the blue field simulation technique (BFS-2000, Oculix Sarl, Arbaz, Switzerland) (22). The blue field entoptic phenomenon is defined as the perception of leukocytes flowing through the subject’s perimacular retinal capillaries. If the fundus is illuminated with blue light with a center wavelength of 430 nm and a narrow optical spectrum, many tiny corpuscles can be observed flowing around swiftly in an area of 10 to 15° of arc radius centered at the fovea. Most likely, this phenomenon is caused by the fact that short-wavelength light is almost totally absorbed by hemoglobin and therefore by red, but not white, blood cells. Thus the passage of a white blood cell through a capillary loop close to the photoreceptors is perceived as a wandering corpuscle.

For determination of retinal hemodynamic parameters, a simulated particle field on a video monitor was shown to the subjects under study. By comparison with their own entoptic observation, subjects adjusted the density and the mean flow velocity. By comparison with their own observations, subjects adjusted the density and the mean flow velocity. Each measurement consisted of at least five matching tests, and the means of velocity and density were calculated. Only values with a standard devia-

<table>
<thead>
<tr>
<th>Table 1. Baseline hemodynamic parameters</th>
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<tr>
<td><strong>Placebo</strong></td>
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<tr>
<td>FPA, µm</td>
</tr>
<tr>
<td>RBF, arbitrary units</td>
</tr>
<tr>
<td>PSV, cm/s</td>
</tr>
<tr>
<td>EDV, cm/s</td>
</tr>
<tr>
<td>SBF, arbitrary units</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 10). FPA, fundus pulsation amplitude; RBF, retinal blood flow; PSV, peak systolic velocity in the ophthalmic artery; EDV, end diastolic velocity in the ophthalmic artery; SBF, subcutaneous blood flow; TG, triglyceride.
tion (SD) of <15% were accepted as accurate. Because this depends on the skill of the volunteers, subjects who did not reach a SD lower than 15% at enrollment were excluded from the trial.

Sonography of the ophthalmic artery. Peak systolic flow velocity (PSV) and end diastolic flow velocity (EDV) were measured in the ophthalmic artery at the point where it crosses the optic nerve, −25 mm posterior the globe (14). Blood flow velocity was assessed with color Doppler imaging using a 7.5-MHz probe with pulsed Doppler device and simultaneous ECG recording (CFM 750, Vingmed Sound, Horten, Norway).

Subcutaneous blood flow. Regional blood flow of the skin was assessed at baseline and every 45 min by laser Doppler flow technique (Moor Instruments, Devon, UK). The laser Doppler system incorporates a low-power, solid state infrared laser diode as a source of coherent light. An optical fiber delivers the light at a penetration of ~1 mm³ in the tissue. Blood flow sampling is restricted to subcutaneous vessels and unaffected by underlying muscle nutritive flow variables. Frequency and power of the reflected photons are analyzed to yield estimations of blood volume and blood flow velocity (12). For estimation of subcutaneous blood flow, the probe head was applied to the skin over the deltoid muscle; before the start of the measurements, we ensured that the signal was not disturbed by arm movements.

Data Analysis

Data are presented as means ± SE. The effects of heparin (pilot study) on hemodynamic parameters were analyzed with Friedman ANOVA. The effect of FFA/triglyceride elevation on outcome parameters was analyzed with repeated-measure ANOVA versus placebo. Post hoc analysis was done using Bonferroni’s correction for multiple comparisons. A P value of <0.05 was considered the level of significance.

RESULTS

Effect of FFA/Triglyceride Elevation

No differences in baseline hemodynamic parameters were observed between FFA/triglyceride elevation and placebo (Table 1). Baseline plasma concentrations of glucose, insulin, FFA, and triglycerides were comparable between both study days. Plasma concentrations of insulin, glucose, FFA, and triglycerides during triglyceride/heparin or placebo infusion are listed in Table 2. As expected, plasma FFA and triglyceride concentrations increased in response to the triglyceride/heparin infusion, whereas insulin plasma concentrations remained unchanged on both study days. The mean glucose infusion rate during FFA/triglyceride elevation (0.30 ± 0.05 mg·kg⁻¹·min⁻¹) was significantly lower compared with the placebo day (0.74 ± 0.13 mg·kg⁻¹·min⁻¹, P = 0.015). In two volunteers, glucose concentrations rose to 8.3 and 10.0 mM without any infusion of glucose during FFA/triglyceride elevation, whereas plasma glucose concentrations in the other subjects remained within the euglycemic range.

Placebo did not affect systemic, ocular, or subcutaneous hemodynamic variables (Table 3). Plasma FFA/triglyceride elevation increased FFA (+25.0 ± 2.7% vs. baseline, P < 0.0001 vs. placebo) and retinal blood flow (+60.1 ± 22.6% vs. baseline, P < 0.013 vs. placebo), reaching highest values at 360 min (Fig. 1). Similarly, PSV in the ophthalmic artery was increased (27.0 ± 7.5% vs. baseline, P < 0.0006 vs. placebo) with maximum effect at 225 min, whereas EDV was not affected. Triglyceride/heparin infusion also increased skin blood flow (+143.7 ± 38.0% vs. baseline, P < 0.001 vs. placebo, Fig. 2). Mean blood pressure and PR remained unchanged, whereas pulse pressure amplitude increased (+17.1 ± 4.7% vs. baseline, P < 0.019 vs. placebo) during triglyceride/heparin administration (Table 3).

Table 2. Plasma concentrations of FFA, TG, glucose, and insulin during placebo and TG/heparin infusion

<table>
<thead>
<tr>
<th>Study</th>
<th>0 Min</th>
<th>45 Min</th>
<th>180 Min</th>
<th>360 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FFA, mM</strong></td>
<td>Placebo</td>
<td>0.16 ± 0.02</td>
<td>0.24 ± 0.04</td>
<td>0.30 ± 0.07</td>
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<tr>
<td></td>
<td>TG/heparin</td>
<td>0.29 ± 0.07</td>
<td>2.20 ± 0.15*</td>
<td>2.86 ± 0.20*</td>
</tr>
<tr>
<td><strong>TG, mg/dl</strong></td>
<td>Placebo</td>
<td>77 ± 13</td>
<td>61 ± 7</td>
<td>51 ± 4</td>
</tr>
<tr>
<td></td>
<td>TG/heparin</td>
<td>64 ± 6</td>
<td>199 ± 21*</td>
<td>193 ± 20*</td>
</tr>
<tr>
<td><strong>Glucose, mM</strong></td>
<td>Placebo</td>
<td>5.44 ± 0.22</td>
<td>4.61 ± 0.11</td>
<td>5.72 ± 0.22</td>
</tr>
<tr>
<td></td>
<td>TG/heparin</td>
<td>4.88 ± 0.17</td>
<td>4.88 ± 0.17</td>
<td>6.83 ± 0.33*</td>
</tr>
<tr>
<td><strong>Insulin, pM</strong></td>
<td>Placebo</td>
<td>39 ± 5</td>
<td>31 ± 3</td>
<td>25 ± 3</td>
</tr>
<tr>
<td></td>
<td>TG/heparin</td>
<td>35 ± 4</td>
<td>35 ± 3</td>
<td>33 ± 5</td>
</tr>
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Values are means ± SE (n = 10). *P < 0.05 for significant changes.

Effect of Heparin Per Se

Plasma concentrations of insulin and glucose did not change from baseline during heparin administration.

Table 3. Systemic hemodynamic parameters during placebo and TG/heparin infusion

<table>
<thead>
<tr>
<th>Study</th>
<th>0 Min</th>
<th>90 Min</th>
<th>180 Min</th>
<th>270 Min</th>
<th>360 Min</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean arterial pressure, mmHg</strong></td>
<td>Placebo</td>
<td>74.7 ± 7.1</td>
<td>78.0 ± 8.7</td>
<td>77.4 ± 9.9</td>
<td>76.4 ± 1.5</td>
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<tr>
<td></td>
<td>TG/heparin</td>
<td>80.7 ± 6.0</td>
<td>79.5 ± 6.6</td>
<td>78.3 ± 6.8</td>
<td>80.5 ± 6.4</td>
</tr>
<tr>
<td><strong>Pulse pressure amplitude, mmHg</strong></td>
<td>Placebo</td>
<td>57.3 ± 1.9</td>
<td>52.3 ± 2.0</td>
<td>52.5 ± 3.7</td>
<td>52.9 ± 3.2</td>
</tr>
<tr>
<td></td>
<td>TG/heparin</td>
<td>53.7 ± 2.5</td>
<td>54.6 ± 2.6</td>
<td>58.8 ± 1.7</td>
<td>60.0 ± 1.9</td>
</tr>
<tr>
<td><strong>Pulse rate, beats/min</strong></td>
<td>Placebo</td>
<td>66 ± 2</td>
<td>61 ± 3</td>
<td>60 ± 3</td>
<td>63 ± 4</td>
</tr>
<tr>
<td></td>
<td>TG/heparin</td>
<td>63 ± 3</td>
<td>60 ± 3</td>
<td>64 ± 3</td>
<td>60 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE (n = 10).
Plasma concentrations of FFA ($P < 0.005$) and triglycerides ($P < 0.001$) decreased during administration of heparin. Heparin did not affect FPA ($P = 0.20$), retinal blood flow ($P = 0.45$), PSV ($P = 0.12$), EDV ($P = 0.06$), and subcutaneous blood flow ($P = 0.25$).

**DISCUSSION**

These results indicate that elevation of plasma FFA and triglycerides markedly increases pulsatile choroidal blood flow, retinal blood flow, and PSV in the ophthalmic artery supplying the eye. Triglyceride/heparin infusion also induced a pronounced increase in local skin blood flow over the deltoid muscle. This is compatible with the observation that FFA/triglyceride elevation induces vasodilation in large vessels (30). It extends previous reports in so far as FFA/heparin infusion also exerts marked vasodilatory effects in the microvasculature of the eye and skin. In addition to this hemodynamic response, there is evidence that FFA/triglyceride elevation alters endothelium-dependent and endothelium-independent vasodilator responses, although the exact nature of this effect is still a matter of debate. FFA dose dependently blunted the metacholine-induced but not sodium nitroprusside-induced vasodilation in the leg, indicating an impairment of endothelial-dependent but not endothelial-independent vasodilation (30). On the other hand, Lundman et al. (15) observed impairment of both endothelial-dependent and endothelial-independent vasodilation in the brachial artery during FFA/triglyceride elevation using a high-resolution ultrasound technique. In the dorsal hand vein, FFA/triglyceride elevation augmented endothelium-dependent vasodilation in response to acetylcholine and metacholine via a cyclooxygenase-dependent pathway, but it did not affect endothelium-independent vasodilation (31). Whether the effect of FFA/triglyceride elevation on endothelial function is directly related to the vasodilator properties observed in the present study remains to be shown.

Several studies indicate that FFA may have an impact on the l-arginine/nitric oxide (NO) pathway, but the exact mechanisms are unclear. In vitro oleic acid causes a concentration-dependent decrease in NO synthase activity in pulmonary artery endothelial cells (6). On the other hand, FFA/triglyceride exposure was recently shown to decrease insulin-stimulated phosphatidylinositol 3-kinase activity, which could be respon-
sible for the reduction in skeletal muscle glucose uptake and glycogen synthesis (8, 24). Interestingly, it has been hypothesized that inhibition of this enzyme is required for NO production and that it induces expression of inducible NO synthase (19). However, a direct link between FFA and NO production cannot be deduced.

The dose of the triglyceride/heparin infusion was identical to that of recent studies on local leg blood flow (30) or on muscle glucose metabolism in healthy subjects (8, 23), and it induced a comparable increase in plasma FFA concentrations. Plasma concentrations achieved in the present study are higher than generally observed in patients with diabetes mellitus, but they may be found in patients with severe insulin resistance and/or lipid disorders. Moreover, it is of note that ex vivo lipolysis may be extensive (33), and overestimation by −28% of plasma FFA concentrations may occur under conditions of lipid/heparin infusion (11). This indicates that the actual plasma FFA levels were much closer to those of insulin-resistant subjects.

Similar to the eye, we also observed an increase of subcutaneous blood flow during FFA/triglyceride elevation that was even more pronounced. This is in contrast to results obtained in subcutaneous adipose tissue of dogs and minipigs (3, 4) and may either be related to species differences or to differences in experimental setup. In early type 2 diabetes, both endothelial-dependent and endothelial-independent vasodilation in the skin are impaired, whereas basal skin blood flow is not different from normal conditions (17). However, it has to be considered that in our study, only transient FFA/triglyceride elevation was implemented, and that other pathological processes like glycation might also contribute to the development of chronic endothelial dysfunction in diabetes mellitus.

Alterations in local ocular and skin blood flow during triglyceride/heparin infusion may result either from local changes in vascular resistance or from changes in systemic hemodynamics as induced by increased FFA/triglyceride concentrations. Indeed, there is evidence that acute FFA/triglyceride elevation increases left ventricular ejection fraction (18). In the present study, SBP, DBP, and PR did not change significantly during FFA/triglyceride elevation, which is in accordance with previous findings (30). A small increase in cardiac output during triglyceride/heparin infusion, which may be supported by the observation of increased pulse pressure amplitude, cannot be excluded in our experiments. Local blood flow in the eye is, however, dependent on ocular perfusion pressure and local vascular resistance. Hence, the marked increase in ocular blood flow after FFA/triglyceride elevation most likely does not result from a systemic hemodynamic effect, but rather reflects a decrease in vascular resistance in the retina and choroid.

This study also found that heparin per se had no effect on ocular, skin, or systemic hemodynamic parameters, although heparin was previously shown to increase NO production in vitro and in vivo (13). However, we cannot decide whether the increase in plasma concentrations of FFA or triglycerides was responsible for the observed hemodynamic changes.

In conclusion, short-term plasma FFA/triglyceride elevation induces 1) a pronounced increase in choroidal blood flow and 2) retinal blood flow as well as 3) a rise in skin blood flow. These effects likely reflect local vasodilation in these vascular beds and may play a role in the development of ocular vascular complications in diabetes mellitus.

Perspectives

Elevation of FFA/triglycerides acutely increases blood flow in the eye and skin as previously shown in the leg where FFA also alters vasodilator responses of endothelium-dependent and endothelium-independent systems (15, 20). This suggests a shift or an imbalance of vascular reactivity, which may contribute to pathological changes in blood vessels. Because the present study focused on the effect of short-term plasma FFA elevation in healthy subjects, a direct link between hemodynamic effects of FFA and pathophysiological mechanisms in insulin-resistant states, like type 2 diabetes mellitus, obesity, and lipid disorders that are associated with chronic but moderate FFA elevation (1, 2, 21), remains to be shown.

The following considerations may give a rationale for further investigations in this field. There is evidence that endothelial function is impaired in patients with long-standing diabetes mellitus (5, 9, 16, 26). In type 2 diabetes mellitus, insulin resistance (24) may at least in part account for endothelial dysfunction, but the mechanism behind impaired vascular reactivity is not fully understood. It is of note that in insulin-resistant subjects, the impairment of endothelium-dependent vascular reactivity is similar to the effect of a combined infusion of triglycerides and heparin in lean healthy volunteers (29, 30). This suggests that elevated plasma FFA may induce endothelial dysfunction as observed in obese insulin-resistant subjects and could therefore play a role in diabetic vasculopathy.

Within the eye, the FFA/triglyceride-induced rise in blood flow is more pronounced in the choroid than in the retina. Interestingly, retinal blood flow is increased in the early stages of diabetic retinopathy, which is considered to play a role in the development of retinal damage (10, 28). However, a direct link between ocular perfusion abnormalities in patients with type 2 diabetes mellitus and plasma FFA concentrations remains to be established.

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HEMODYNAMIC EFFECTS OF FFA


