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ORIGINAL ARTICLE

Microangiopathy and visual deficits characterize the retinopathy of a spontaneously hypertensive rat model with type 2 diabetes and metabolic syndrome

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Retinopathy has been increasing in prevalence as a consequence of type 2 diabetes and a cluster of coexisting risk factors characterized as the metabolic syndrome. However, the combined effects of these conditions on the retina are poorly understood. Therefore, we focused on the spontaneously hypertensive corpulent rat (SHR/N-cp), a model with type 2 diabetes, obesity and features of the metabolic syndrome to characterize retinal changes at a structural and functional level. SHR/N-cp males at 4 and 8 months of age were used in this study. Metabolic parameters and blood pressure were measured by standard methods. Morphology was investigated by histological techniques supplemented by nicotinamide adenine dinucleotide phosphate-diaphorase staining of whole mounts and fluorescein angiography to analyze the retinal vasculature. The *in vivo* function of the retina was examined by electroretinography (ERG). Obese SHR/N-cp rats were hypertensive and showed significant increases in body weight, serum levels of glucose, triglycerides, total cholesterol and urinary glucose excretion compared with lean controls ($P<0.01$ for each). Histology indicated an overall intact integrity of the retina and aspects of microangiopathy in obese SHR/N-cp rats. ERG revealed intact processing of light signals but significantly decreased amplitudes of b-waves for all ($P<0.01$) and of a-waves for some examined light intensities ($P<0.05$). Oscillatory potentials were significantly protracted ($P<0.01$), whereas amplitudes were not reduced. Microangiopathy and electroretinographic deficits combine to produce an early non-proliferative retinopathy phenotype in the obese SHR/N-cp rats. Thus, this model represents a valuable experimental tool to obtain further insights into the mechanisms of retinopathy in the context of obesity, type 2 diabetes and metabolic syndrome.
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INTRODUCTION

Diabetic retinopathy is the most common and specific microvascular complication of diabetes.[1] Hyperglycemia represents the major modifiable risk factor of diabetic retinopathy, as demonstrated by the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study for type 1 and type 2 diabetic patients, respectively.[2,3] In addition, the results of United Kingdom Prospective Diabetes Study have clearly demonstrated the benefit of blood pressure control for hypertension in type 2 diabetic patients in terms of reducing risk for both deterioration of retinopathy and visual acuity.[4] This result is supported by experimental studies with spontaneously hypertensive rats, rendered diabetic by streptozotocin (STZ), which have demonstrated that the concomitance of diabetes and hypertension leads to aggravated early inflammatory events,[5,6] oxidative stress,[7,8] neurodegeneration and mitochondrial dysfunction[8] in the retina. Notably, these effects can be reduced by antihypertensive drug treatment.[6,8] Furthermore, there is increasing evidence for an association of hyperlipidemia with diabetic retinopathy.[9] Taken together, these results implicate the cluster of risk factors known as the metabolic syndrome in retinopathy. Furthermore, in clinical practice, obese patients with type 2 diabetes represent the vast majority of diabetic patients, and they exhibit additional cardiometabolic abnormalities, including hyperlipidemia and hypertension, which are core components of the metabolic syndrome.[10,11] Nevertheless, despite the increasing prevalence of metabolic syndrome and type 2 diabetes worldwide, its combined effects on the retina are still not well characterized. We therefore set out to address this point in an experimental setting by investigating the retina in the obese and spontaneously hypertensive corpulent (SHR/N-cp) rat model.[12] This model combines obesity, type 2 diabetes, hypertension and hyperlipidemia[13] and exhibits a wide range of target organ damage; atherosclerosis,[12] hepatic steatosis,[14] pancreatic islet cell hyperplasia,[15]

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cardiomyopathy[16] and nephropathy[17,18] have been described in SHR/N-cp. Furthermore, this model demonstrates an important feature of the metabolic syndrome, that is, insulin resistance,[19] which has also gained importance with regard to the pathogenesis of retinopathy, particularly retinal neovascularization.[20] Furthermore, SHR/N-cp resembles the slow progression of target organ damage in metabolic syndrome that can be observed during the lifespan of the animals over several months.[12] In this regard, SHR/N-cp contrasts sharply with the widely used STZ)-induced diabetes rat model.[21] Because STZ toxicity rapidly leads to destruction of the β-cells in the pancreas with acute insulin deficiency, loss of body weight and a pronounced reduction of lifespan,[22] this widely used model imitates type 1 diabetes but is quite different from the pathophysiology observed in type 2 diabetes and the metabolic syndrome.

Therefore, we selected the obese SHR/N-cp rat model because it offers the opportunity to analyze changes in retinal morphology and function in an experimental setting characterized by the combination of type 2 diabetes and features of the metabolic syndrome.

METHODS

Animals

The SHR/N-cp rats were obtained from our colony at the Charité—Universitätsmedizin Berlin, which was established with breeders that were a gift from O Tulp at the Department of Nutrition and Food Sciences, Drexel University, Philadelphia, PA, USA. This rat strain was originally derived by mating a male Koletzky rat[12] that was heterozygous for the corpulent gene mutation (*cp*/+) to a female SHR rat of the Okamoto strain, with subsequent backcrosses to eliminate the non-*cp* genes of the Koletzky strain. Therefore, the SHR/N-cp is obese due to the *cp* mutation, which has been identified as a functional null mutation of the leptin receptor.[23] Because corpulent rats are infertile the rats are bred by mating heterozygotes. Mating yields three genotypes, namely, homozygous obese (cp/cp), heterozygous lean (cp/+) and homozygous lean (+/+), in a ratio of 1:2:1. All animals in this study were male, and as controls for the homozygous obese rats, only homozygous lean animals were used. Animals were housed with a fixed light cycle daily from 8:00 to 20:00 hours at 22 ± 1 °C in standard box cages. Ketamine (120 mg kg^{-1}) and xylazine (10 mg kg^{-1}) were intraperitoneally injected to anesthetize the animals. Animals were killed by carbon dioxide inhalation. All experiments were conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research, the local ethics review board for the use of laboratory animals, and conformed to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication no. 85-23, revised 1996).

Parameters of metabolic syndrome

The serum and urine parameters as shown in Table 1 were measured in SHR/N-cp rats at 8 months of age (n=9 obese, n=9 lean). Systolic blood pressure was measured in awake animals by the tail-cuff method as previously reported.[24] Details appear in the Supplementary Material online.

Morphology

Enucleated eyes of SHR/N-cp animals (4 and 8 months of age; n=3 for each genotype at each age) were used for histological analysis with paraffin sections. Nicotinamide adenine dinucleotide phosphate (NADPH)-diaphorase (NADPH-d) staining of whole mounts[25] was performed with three obese and three lean SHR/N-cp rats at 4 months and five obese and five lean SHR/N-cp rats at 8 months of age. Densities of NADPH-d-stained microvessels were determined and quantified according to Robison *et al.*[26] in both strains at 8 months of age (n=5 each). The ratio of arteriolar to venous diameter was measured in obese and lean animals (n=4 each) according to Mori *et al.*[27] Fundus fluorescein angiography was performed in 8-month-old animals of both strains (n=4 each) by intravenous injection of sodium fluorescein. Details appear in the Supplementary Material online.

Table 1 Characteristics of obese *vs.* lean SHR/N-cp (N=9)

	Obese SHR/N-cp	*Lean SHR/N-cp*	P-*values*
Metabolic syndrome			
Body weight (g)	537 ± 24	338 ± 73	<0.001
Systolic blood pressure (mm Hg)	181 ± 2	177 ± 3	NS
Glucose in serum (mmol l^{-1})	19 ± 4	9 ± 3	<0.001
Glucose excretion in urine (mmol per 24 h)	9.89 ± 1.15	0.03 ± 0.01	<0.01
Glycosylated fructosamine in serum (μmol l^{-1})	163 ± 18	136 ± 9	<0.001
Triglycerides in serum (mmol l^{-1})	4.51 ± 1.2	0.93 ± 0.18	<0.001
Total cholesterol in serum (mmol l^{-1})	4.75 ± 0.70	1.88 ± 0.23	<0.001
Renal function			
Creatinine in serum (μmol l^{-1})	45 ± 4	47 ± 3	NS
Creatinine clearance (ml min^{-1})	1.4 ± 0.3	1.2 ± 0.3	NS
Albumin excretion in urine (mg per 24 h)	38.7 ± 2.9	1.8 ± 1.3	<0.001

Abbreviation: NS, not significant (P>0.05).
Data are given as mean ± s.d., P-values were calculated by two-tailed t-test in the groups obese *vs.* lean SHR/N-cp.

Electroretinography

For electroretinography (ERG) measurements, 8-month-old obese and lean SHR/N-cp rats (n=6 each) were used. Standard electroretinographic measurements were performed simultaneously on both eyes with scotopic flash ERG, scotopic oscillatory potentials, photopic 30-Hz flicker ERG, photopic flash ERG and photopic oscillatory potentials. Details appear in the Supplementary Material online.

Statistical methods

Statistical group differences between obese and lean SHR/N-cp animals were analyzed by Student's t-test. The level of significance was set at P<0.05. Data are given as mean ± s.d.

RESULTS

Metabolic syndrome parameters

Parameters of metabolic syndrome in obese SHR/N-cp rats at 8 months of age in comparison with the lean controls are displayed in Table 1.

Obese SHR/N-cp rats had a significantly higher body weight (P<0.001) compared with lean SHR/N-cp. They were diabetic, as indicated by a significantly higher serum glucose level (P<0.001) compared with lean controls. In addition, 24-h urinary glucose excretion and glycosylated fructosamine were significantly elevated (P<0.01). Obese SHR/N-cp rats were hyperlipidemic with a significantly higher level of serum triglycerides (P<0.001) and cholesterol (P<0.001) compared with lean SHR/N-cp. Both lean and obese rats were hypertensive, and no significant blood pressure differences between the two groups were observed.

Renal parameters

Serum creatinine and creatinine clearance were comparable in both groups of animals. Urinary albumin excretion per 24 h was approximately 20-fold higher in obese *vs.* lean animals (Table 1).

Retinal morphology

Hematoxylin and eosin-, azan-, sirius red- and periodic acid-schiff reagent-stained paraffin sections were examined by light microscopy at 4 and 8 months of age. The integrity of the laminar structure of the retina was intact in both groups of animals. There were no

neovascularizations and no exudates (Figures 1A and B). At 4 months of age, a fine microvasculature of the retina was evident in obese and lean animals from the blue-stained NADPH-d-positive endothelial cells (Figure 2). The closely meshed microvasculature was similar in density and shape in obese *vs.* lean animals. At 8 months of age, the meshwork of stained microvessels decreased in density in obese animals (Figures 2e and g) compared with controls (Figures 2f and h). At this time point, the mean density of NADPH-d-positive microvessels in obese animals was 0.67 ± 0.22 times that of lean animals, and this difference was statistically significant ($P<0.05$). This indicates a loss of NADPH-d-positive endothelial cells in segments of the microvessels in obese animals. The mean ratio of arteriolar to venous diameter in 8-month-old animals was 0.64 ± 0.10 in obese and 0.75 ± 0.08 in lean animals, which was a significant reduction of 15% in obese *vs.* lean animals ($P<0.05$). Comparing the mean values of arteriolar and venular diameters in obese *vs.* lean animals, there was a 9.7% decrease in arteriolar diameters and a 6.8% increase in venular diameters, but these differences were not significant.

Fundus fluorescein angiograms detected no specific alterations in obese *vs.* lean animals in morphology or time course. Specifically, there were no specific zones with hypo- or hyperfluorescence or

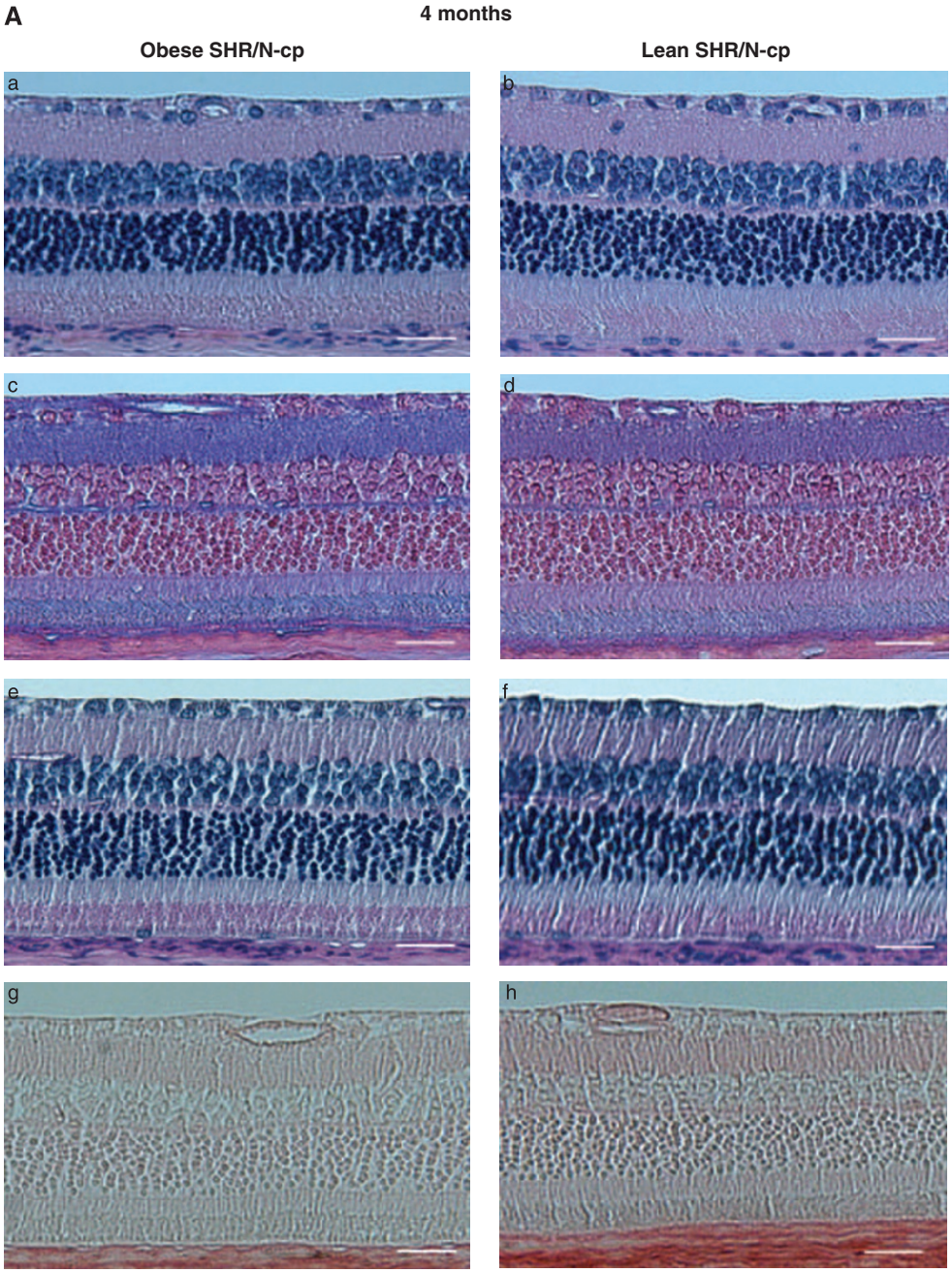

Figure 1 Metabolic syndrome did not affect the integrity of the retina in obese SHR/N-cp as indicated by paraffin sections stained with hematoxylin and eosin (a), azan (c), periodic acid-schiff reagent (e) and sirius red (g) at 4 months (**A**) and 8 months (**B**) of age; lean SHR/N-cp as controls (b, d, f, h, respectively), scale bars 40 μm.

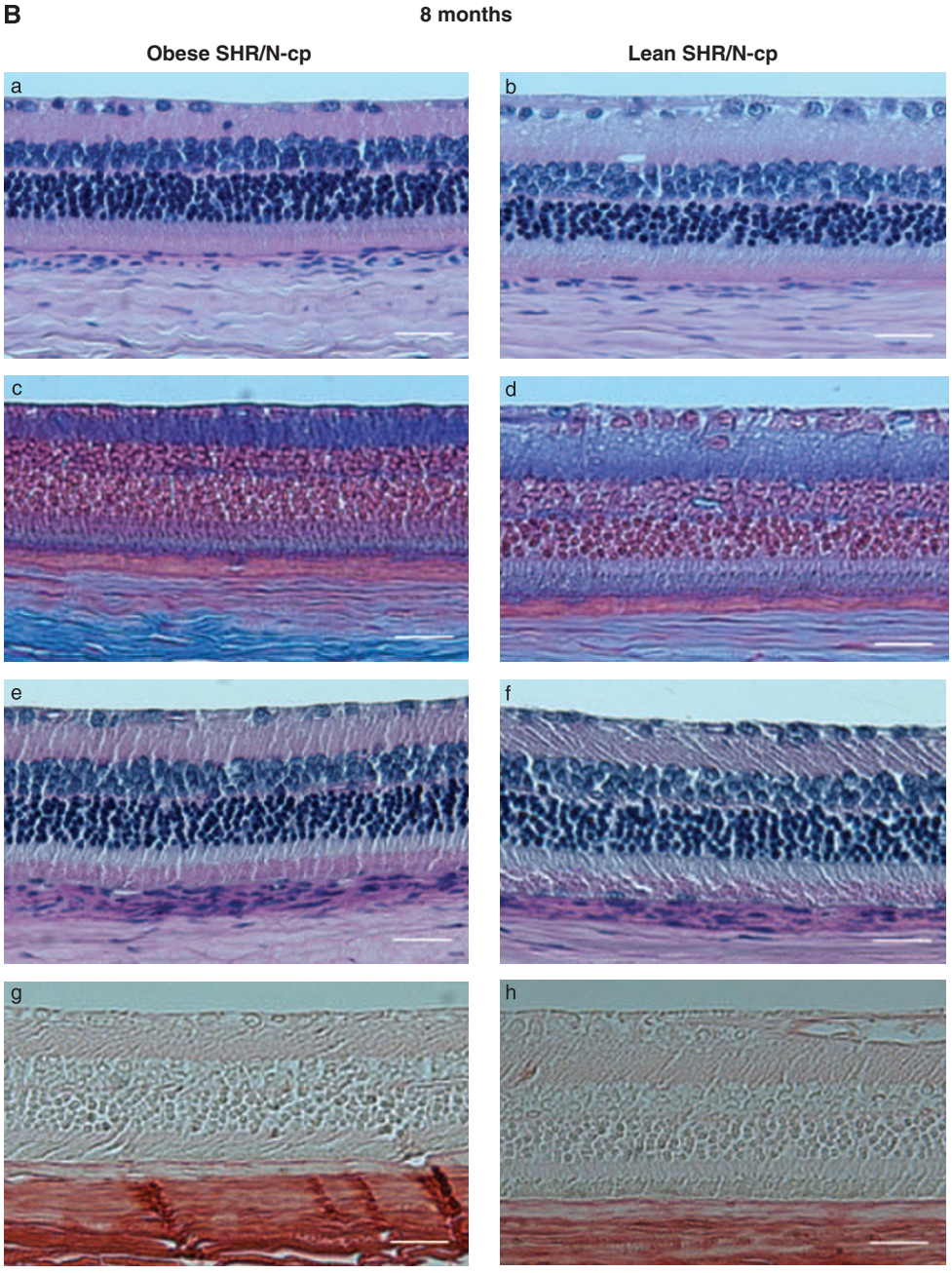

Figure 1 Continued.

fluorescein leakage from microvessels in either group (Figure 1 in Supplementary Material online).

Electroretinography

Electroretinography (ERG) measurements were performed in six lean and six obese SHR/N-cp rats. Overall, the appearance of the ERG waveforms obtained in the animals revealed no major abnormalities (Figure 3). However, visual comparison of the waveforms showed smaller amplitudes in obese rats, whereas the rates of retinal responses to visual stimuli appeared to be quite similar.

Inspection of the numerical parameters obtained from waveform analysis of all animals confirmed this impression (Figure 4). The amplitudes of scotopic a-waves were significantly smaller in obese rats for only some light intensities (Figure 4a; $P<0.05$). The amplitudes of scotopic b-waves were significantly smaller in obese *vs.* lean rats for all investigated light intensities (Figure 4a; $P<0.01$). By contrast, the latencies of scotopic a-waves and b-waves were significantly increased in the obese *vs.* lean animals only for some light intensities (Figure 4a, $P<0.05$).

Amplitudes of oscillatory potentials did not show significant differences. Latencies were again slightly longer in obese animals, and the differences were significant in both scotopic and photopic oscillations (Figure 4b). Photopic b-wave amplitudes and photopic 30-Hz flicker amplitudes were significantly larger in lean rats (Figure 4c).

Finally, the ratios among the amplitudes of a-waves, b-waves and oscillatory potentials were compared (Figure 4d). The b/a ratio was significantly higher in lean rats, whereas the OP/b ratio was

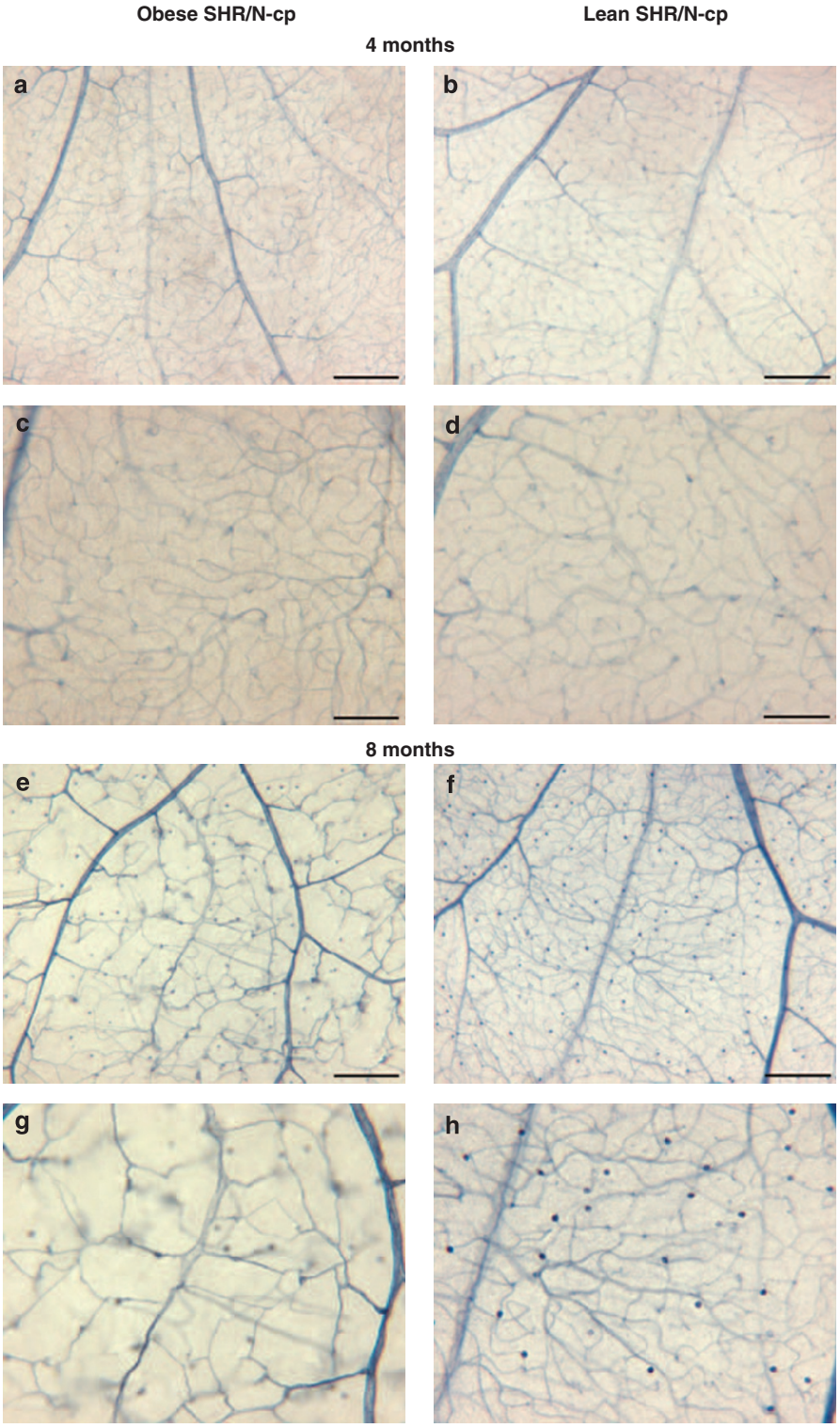

Figure 2 NADPH-d staining of whole mount retinas revealed a fine-meshed capillary network in obese (**a**, **c**) and lean (**b**, **d**) SHR/N-cp at 4 months of age. The meshwork of stained capillaries is less dense in obese SHR/N-cp at 8 months of age (**e**, **g**) relative to the lean control (**f**, **h**); scale bars for **a**, **b**, **e**, **f** is 200 μm; for **c**, **d**, **g**, **h** is 100 μm.

significantly higher in obese rats. No significant difference could be seen in the OP/a ratio (Figure 4d).

Amplitudes of a-waves and b-waves measured in lean and obese rats at different light intensities were used to calculate the Naka-Rushton parameters using Equation (1), as shown in Supplementary Materials. The ERG data are summarized in Table 2. The most prominent difference was seen in the R_{max} values of the b-waves, where higher values were obtained for the lean rats. Although the R_{max} values were

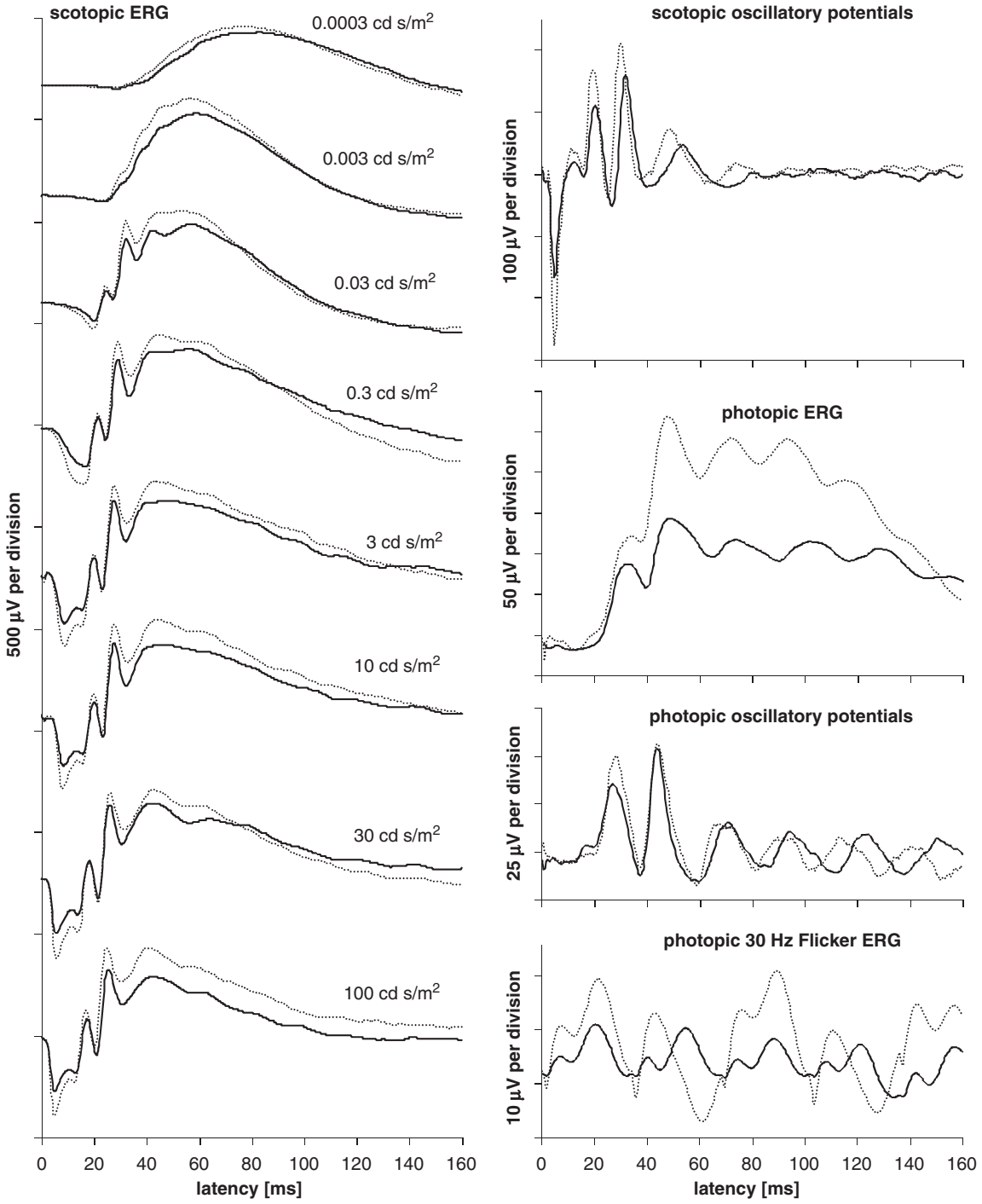

Figure 3 Comparison of typical waveforms obtained in a lean (dotted lines) and obese SHR/N-cp (solid lines) obtained by different methods as indicated. Light intensities applied in scotopic electroretinography (ERG) measurements are indicated nearby the waveforms.

also higher in lean rats in the case of the a-waves, the difference was not significant. Overall, the values of the ERG parameters showed remarkably higher variability in the obese animals.

DISCUSSION

Both nephropathy and retinopathy represent characteristic long-term microvascular complications in diabetes with profound effects on morbidity, mortality and quality of life in affected patients.[1,28] Although both conditions share common disease mechanisms,[29] several differences in pathogenesis have been reported.[30] Moreover, even within one condition, the manifestation and progression of the organ damage may depend on existing comorbidities, such as hypertension[4] and dyslipidemia.[9] Thus, Gross *et al.*[17] previously demonstrated striking differences in the renal pathology between the STZ model of diabetes and the SHR/N-cp model of type 2 diabetes. They reported that diabetic animals in response to STZ treatment exhibited only modest glomerulosclerosis, tubulointerstitial damage and albuminuria, whereas the SHR/N-cp animals showed more striking

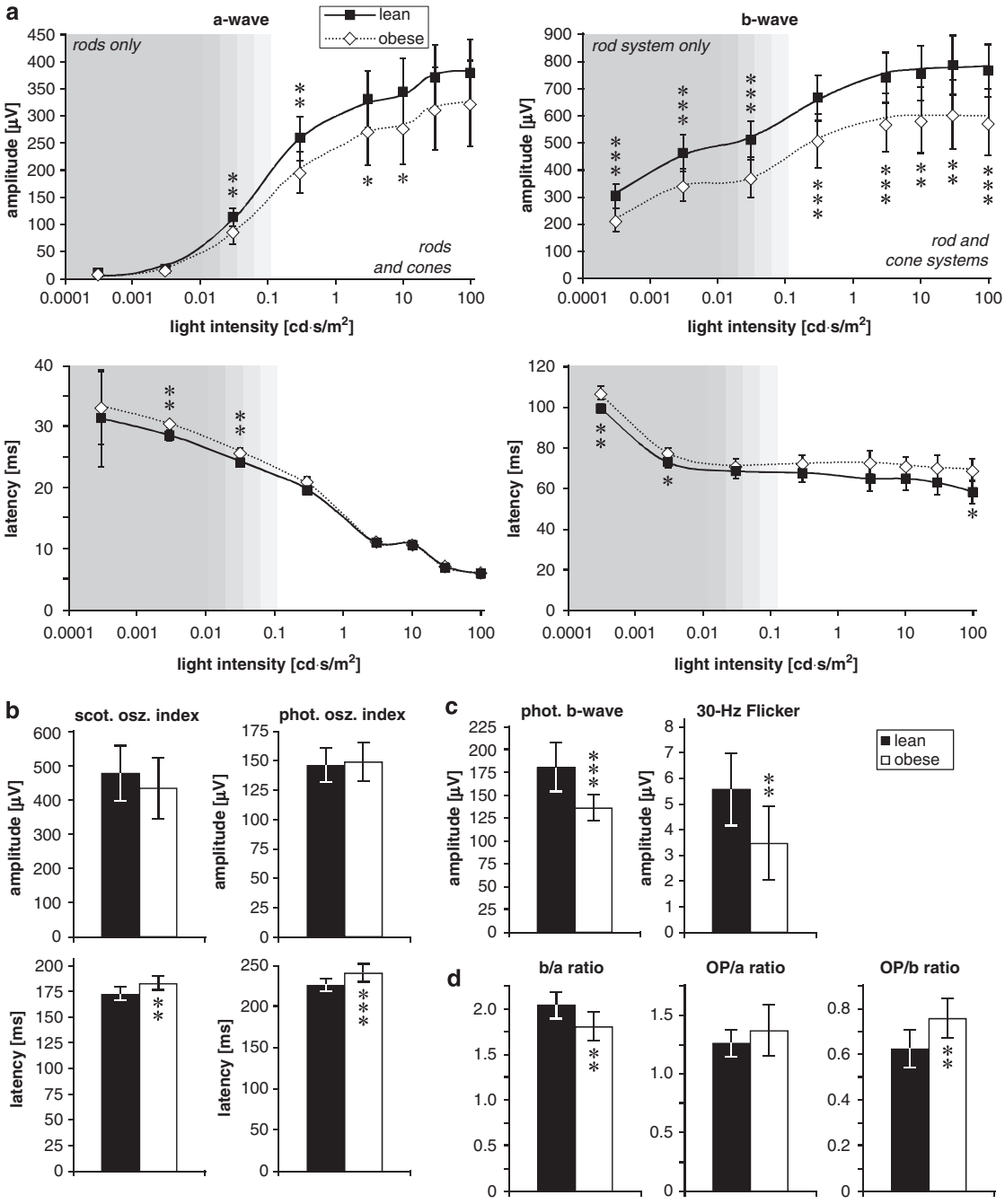

Figure 4 Comparison of electroretinography (ERG) parameters obtained in lean and obese SHR/N-cp. (**a**) Amplitudes and latencies of scotopic a-waves and b-waves. The curves in the diagrams displaying amplitudes were calculated using the Naka-Rushton parameters listed in Table 2. The curves in the diagrams displaying latencies serve to guide the eye and represent no model. (**b**) Amplitudes and latencies of scotopic and photopic oscillatory potentials, expressed as corresponding indices. (**c**) Amplitudes of photopic b-waves and 30-Hz Flicker ERG. (**d**) Values of ratios of different amplitudes as indicated. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$.

glomerular and tubulointerstitial lesions combined with more pronounced albuminuria. In this regard, the aim of this study was to investigate retina pathology in the SHR/N-cp model that combines type 2 diabetes and features of the metabolic syndrome, including obesity, hypertension and hyperlipidemia as well as insulin resistance.[13,15,31]

In contrast to the more pronounced target organ damage previously reported in the cardiovascular system[12] and kidney,[17,18] histological analysis in this study revealed an intact integrity of the retina in obese animals. Specifically, azan and sirius red staining demonstrated no marked difference in the expression of matrix molecules. There were no signs of hard or soft exudates and no neovascularizations into the vitreous (Figures 1A and B). These results suggest that target organ damage of the retina is more subtle compared with changes in peripheral organs, such as the kidney, as previously reported.[17,18] Although we performed no renal histology analysis, our data indicating marked albuminuria in obese SHR/N-cp animals are in agreement with previous findings, in which significant structural changes in the

Table 2 Calculated Naka-Rushton parameters from electroretinographic a-wave and b-wave amplitudes

	Lean SHR/N-cp	*Obese SHR/N-cp*	P-*values*
a-Waves			
$R_{max,1}$	337.99 ± 55.97	291.05 ± 71.82	NS (0.1014)
n_1	0.8511 ± 0.1138	0.7435 ± 0.0880	0.0214
$i_{50,1}$	0.0742 ± 0.0207	0.1023 ± 0.0205	0.0042
$R_{max,2}$	44.61 ± 23.12	34.68 ± 12.08	NS (0.2199)
n_2	4.172 ± 3.249	10.97 ± 5.19	0.0013
$i_{50,2}$	15.36 ± 6.48	25.07 ± 3.57	0.0003
b-Waves			
$R_{max,1}$	436.00 ± 63.69	338.52 ± 75.65	0.0035
n_1	3.3405 ± 1.0317	2.0822 ± 1.0688	0.0102
$i_{50,1}$	0.00023 ± 0.000002	0.00022 ± 0.00005	NS (0.6815)
$R_{max,2}$	346.24 ± 50.89	256.76 ± 101.85	0.0161
n_2	0.7791 ± 0.1928	1.2979 ± 0.7623	0.0396
$i_{50,2}$	0.1481 ± 0.0395	0.1736 ± 0.0674	NS (0.2891)

Abbreviation: NS, difference not significant ($P>0.05$).
Data are given as mean ± s.d., *P*-values were calculated by two-tailed *t*-test in the groups obese *vs.* lean SHR/N-cp.

kidney have been clearly demonstrated in parallel to the albuminuria in the same model.[17] On this basis, we asked how the microvessels were affected in obese SHR/N-cp rats. NADPH-d staining of the microvasculature was reduced by 33% in the retina of 8-month-old obese animals *vs.* controls ($P<0.05$), which can be interpreted as a loss of endothelial integrity in segments of diverse microvessels. This parallels results in the retina during the early stages of STZ-induced diabetes[32] and underscores the contribution of nitric oxide to the pathogeneses of retinopathy in obese animals, as previously demonstrated in diabetic retinopathy in STZ rat retinas.[33] Notably, pericyte loss has also been described as an early pathological feature of diabetic retinopathy.[34] In close contact with retinal capillaries, these cells are important for the tightness of the inner blood–retina barrier[35] and for the integrity of the endothelial cells.[34] An impaired cellular crosstalk of pericytes with endothelial cells has been proposed as one of the initial processes in the course of diabetic retinopathy.[34] In this regard, the fact that changes in pericytes could not be detected with the techniques applied in our study represents a limitation of our study. Nevertheless, on the basis of our observed alterations in the microvasculature of obese animals, future studies might focus on potential changes affecting pericytes by applying more specialized techniques[36,37] and could thereby expand the knowledge of microangiopathy in the context of the metabolic syndrome.

The impairment of microvasculature in obese animals did not result in leakage zones of fluorescein angiography, which would have indicated a profound insufficiency of the inner blood–retina barrier, with implications for medical intervention in humans. By ophthalmoscopy, there were no obvious clinical signs of breakage of the blood–retina barriers, for example, exudates. Nevertheless, minor changes even of the outer blood–retina barrier, which are relevant in human diabetic retinopathy, cannot be ruled out by our investigations but may be detected by vitreous fluorometry.[38] Indirect ophthalmoscopy of living animals revealed that choroidal and retinal vessels were more variable in diameter in obese animals compared with controls at 8 months (not shown). Quantification of the ratio of arteriolar to venous diameter revealed a slightly reduced ratio in obese *vs.* lean animals. Although ocular vasculopathy with narrowing of microvessels has been described in spontaneously hypertensive rat strains,[39] this result may suggest that features of metabolic syndrome aggravate the microvascular changes in this model. Nevertheless, the technique we employed considered only one aspect of microangiopathy in a circumscribed area of the rat retina. Moreover, further aspects of microangiopathy, as they can be investigated in humans over the whole fundus by more sophisticated techniques, were not determined in our rat model.[40]

Taken together, these findings point to the presence of initial microangiopathy in the retina of obese animals. As a consequence of discrete morphological damage in the retina of obese animals, we further set out to address the question of whether functional deficits can be observed in this setting of microangiopathy and in the absence of major structural changes in the retina. As shown in Figure 3, electroretinograms of obese rats showed a normal shape, indicating that processing of light signals with different intensities was principally intact. Therefore, it can be deduced that the obese rats retained their capacity for vision with high complexity, indicating that neuronal networks and the complex interconnections with glial cells were not fundamentally disturbed by metabolic changes in obese animals. In this regard, the above-described morphology with an intact integrity of the retina correlated well with the overall good function according to ERG. However, several distinct analyses, such as scotopic and photopic ERG, the 30-Hz flicker ERG (Figure 3), the decreased b/a ratio, the increased OP/b ratio (Figure 4d) and the decreased b-wave-related R_{max} values (Table 2), point to a clear decrease in b-wave amplitudes, which may principally be due to an impaired function of bipolar or Müller glial cells.[41] Because further sensitive activities of bipolar cells remained intact in the electroretinograms, the Müller cells were the most probable cause for b-wave reductions. Thus, Müller cells may be a critical cell type in the initial pathogenesis of early retinopathy in type 2 diabetes with metabolic syndrome. They may be the origin of the modulation of multiple key functions in the course of retinopathy because they are involved, for example, in angiogenesis,[42] in the maintenance of the blood–retina barriers,[43] in neurotransmitter metabolism[44] and in retinal fluid homeostasis.[43] This finding suggests that Müller cell-related pathogenesis is a characteristic of type 2 diabetes with obesity and metabolic syndrome, because in STZ-induced diabetic rats, the reduction of b-waves typically occurs not before but concomitantly with changes in the amplitudes of oscillatory potentials.[45–47] However, changes in oscillatory potentials in obese animals were restricted to a small but significant increase of latencies (Figure 4b). This characteristic of oscillatory potentials precedes leakage in fluorescence angiography in the STZ-diabetic rat model[48] and therefore is compatible with the mild microangiopathy found in the morphological analysis of this study. In humans, such an ERG pattern is typical for diabetic patients with discrete microangiopathy but not with more profound funduscopic changes, such as hard exudates, which would represent later stages of diabetic retinopathy.[48] In this regard, the increased latency of oscillatory potentials without a reduction in amplitude in obese SHR/N-cp rats together with initial microangiopathy are parallels to early diabetic retinopathy in human.[48,49] The findings in obese animals are completed by a subtle photoreceptor dysfunction, indicated by affected a-wave parameters, similar to the reduction of amplitudes, increased latencies (Figure 4a) and higher a-wave-related i_{50} parameters (Table 2). Remarkably, altered function of photoreceptors has also been described in the STZ-induced diabetic rat model based on different findings.[50–52] In addition, affected a- and b-wave parameters could be a consequence of impaired blood circulation, which is a characteristic of diabetic retinopathy and may therefore be correlated with the morphologically described microangiopathy.[53]

A further striking characteristic of retinopathy in obese animals is its slower progression compared with the insulin-deficient STZ model. This strengthens the idea that due to specific metabolic states, retinopathies in both animals have some fundamental differences, despite their similarities. This is in line with results from clinical studies demonstrating that in addition to hyperglycemia, other metabolic factors and blood pressure are involved in the manifestation and progression of retinopathy in humans.[4,54,55] In this regard, SHR/N-cp together with other non-STZ-based rat models[56–64] are useful tools to dissect the complexity of causative factors and disease mechanisms contributing to the varying spectrum of diabetic retinopathy.[55] Studies in these models have indeed revealed the contrasting impairment of the retina in the presence of cardiometabolic risk factors.[62,63] Intervention during an early stage of the disease is particularly important to prevent manifestations of visual deterioration.[55,65] The latter aspect underscores the value of the SHR/N-cp model, which exhibits characteristics of the early phase of diabetic retinopathy. Therefore, this animal model offers the opportunity to investigate retinopathy at an early stage in a setting of cardiometabolic risk factors, which show increasing prevalence worldwide.

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