Supplementary Methods

Structural and mechanical properties in mesenteric resistance arteries

Second-order branch of mesenteric resistance arteries (MA) were dissected to determine structural and mechanical properties with a pressure myograph (Model P100, Danish Myo-Tech) as previously described [32]. Briefly, after a 30 min equilibration period at 70 mmHg in gassed calcium-free PSS solution at 37°C, a pressure-diameter curve (5-140 mmHg) was obtained and external and internal diameters (D_{i0Ca} and D_{e0Ca}, respectively) were measured. After maximal relaxation in salt solution without calcium ($0Ca^{2+}$), MA segments were fixed at 70 mmHg with 4% paraformaldehyde (in 0.2 mol l^{-1} phosphate buffer, pH 7.2-7.4) at 37ºC for 45 min and stored at 4ºC for confocal microscopy studies. From the D_{e0Ca} and D_{i0Ca} values structural and mechanical parameters were calculated as previously described [32]. Intrinsic wall stiffness was determined by the parameter β, calculated from stress-strain relationship, which is directly proportional to Young´s incremental elastic modulus and a measure of intrinsic stiffness independent geometry.

Elastin content and organization in mesenteric resistance arteries

Elastin content and organization in the external (EEL) and internal elastic laminae (IEL) were studied in intact pressure-fixed second branch mesenteric resistance arteries (MA) with fluorescent confocal microscopy based on the auto fluorescent properties of elastin (excitation 488 nm /emission 500-560 nm) as previously described [32]. Intact arterial segments were mounted on a slide provided with a small well of spacers to avoid artery deformation, filled with citifluor mounting medium (antifadent solution; Citifluor) and visualized which a Leica TCS SP5 confocal system. Serial optical sections (stacks of images) from the adventitia to the lumen were captured with a x63 oil immersion objective using the 488-nm line of the confocal microscopy. A minimum of two stacks of images of different regions were captured in each arterial segment. All the images were taken under identical conditions of laser intensity, brightness and contrast. Quantitative analyses were performed which three randomly selected regions IEL of a least five independent experiments using Image J software. From each stack of serial images, individual projections of IEL were reconstructed to measure total fenestra number and area. Elastin density was estimated from fluorescence intensity values.

Vascular reactivity in the superior mesenteric artery (MA)

The MA was placed in oxygenated physiological salt solution (PSS; 115 mmol l^{-1} NaCl, 4.6 mmol l^{-1} KCl, 2.5 mmol l^{-1} $CaCl_2$, 25 mmol l^{-1} $NaHCO_3$, 1.2 mmol l^{-1} KH_2PO_4, 1.2 mmol l^{-1} $MgSO_4$, 0.01

mmol l^{-1} EDTA and 5.5 mmol l^{-1} glucose) and cleaned of blood and perivascular fat. MA Rings (3 mm long) were suspended on two intraluminal parallel wires, introduced in an organ bath with oxygenated PSS, connected to a Piodem strain gauge for isometric tension recording. Segments were given an optimal resting tension of 1.5 g, which is then readjusted every 15 min during a 60 min equilibration period. Afterwards, segments were incubated with 75 mmol/L KCl to check their contractility and contraction curves to noradrenaline (NA, 10^{-9}-10^{-6} mol l^{-1}) were performed. Relaxation curves to ACh (10^{-9}-10^{-4} mol l^{-1}) were analysed in segments previously contracted with NA at concentrations which varied between 10^{-7} and 10^{-6} mol l^{-1} to ensure a similar pre-contraction level between groups. The nitric oxide synthase inhibitor, N_G-nitro-L-arginine methyl ester (L-NAME, 0.1 mmol l^{-1}), the NADPH oxidase inhibitor, apocynin (0.1mmol l^{-1}) or the catalase inhibitor, 3-amino-1,2,4-triazole (3-AT, $5x10^{-3}$ mol l^{-1}) were incubated 30 min before pre-contraction with NA. The net contribution of NO was assessed by calculating the difference between the AUC in presence and absence of L-NAME. The effect of FIN treatment on the contribution of $O_2^{\cdot-}$ or H_2O_2 to contractile responses was analyzed performing concentration-response curves to NA in presence of apocynin, a ROS scavenger and direct inhibitor of ROS-induced signaling in vascular cells or the catalase inhibitor, 3-AT.

Statistical analysis

Contractile responses are expressed as the percentage of contraction induced by 75 mmol·L-1 KCl. Relaxations are expressed as the percentage of previous contraction elicited by NA. The maximal response (E_{max} values) and the potency (negative logarithm of concentration) producing 50% of maximum response (pD_2 values) were assessed by a non-linear regression analysis of each individual concentration-response curve. AUC were calculated from each individual concentration response curve plot (GraphPadSoftware, California, United States). All values are given as mean ± SEM.

Supplementary results

Finerenone improves endothelial relaxation in MA from MWF rats

Endothelial relaxation to ACh was significantly lower in MA from MWF-C compared with W-C rings (Supplementary Figure 2A and Supplementary Table 2). FIN treatment significantly improved relaxations to ACh in MWF rats reaching control levels (Supplementary Figure 2 and Supplementary Table 2).

Contractions to NA were significantly higher in MWF-C than W-C arteries, and significantly reduced by FIN treatment to control levels (Supplementary Figure 2B and Supplementary Table 2).

Concentration-response curves to NA were increased by L-NAME in all groups (Supplementary Figure 2C and D; Supplementary Table 2) although the increase was significantly higher in MWF-FIN compared with MWF-C rings.

Finerenone reduces superoxide anion and hydrogen peroxide levels in MA from MWF rats

Apocynin, an inhibitor of superoxide productin, significantly reduced NA-induced contractions in W-C, W-FIN and MWF-C arteries. However, the inhibitory effect of apocynin was higher in the MWF-C group (MWF-C, Emax-C=79.2±9.3% *vs* Emax-apocynin=49.3±9.1; $p<0.05$; W-C, Emax-C=55.8±5.2% *vs* Emax-apocynin=52.9±6.4; W-FIN, Emax-C=65.7±5.6% *vs* Emax-apocynin=57.3±7.3%) suggesting a higher contribution of superoxide anions compared to the W groups. Apocynin did not modify contractions to NA in MWF-FIN arteries (Supplementary Figure 3A and B).

Preincubation with 3-AT, a catalase inhibitor, significantly reduced NA-induced contractions in W-C, W-FIN and MWF-C rats. The reduction was, however, more pronounced in the MWF group (MWF-C, Emax-C=79.19±9.3% *vs* Emax-3-AT=52.8±10.6; $p<0.05$; W-C, Emax-C=55.8±5.2% *vs* Emax-3-AT=50.7±4.9; W-FIN, Emax-C=65.7±5.6% *vs* Emax-3-AT=64.5±5.5%). 3-AT did not modify NA-induced contractile responses in MWF-FIN rats (Supplementary Figure 3C and D).