

Supplemental Table 1. Potency of the NO donor Spermine-NONOate in the aorta and size of mesenteric arteries used in the isolated vascular reactivity studies from male and female WT and ecCNP KO mice. n=6.

<i>Genotype</i>	<i>Spermine-NONOate pEC₅₀ (M)</i>	<i>Vessel diameter (μm)</i>
Male WT	6.65±0.04	157±6
Male ecCNP KO	6.80±0.03	151±5
Female WT	6.48±0.04	156±10
Female ecCNP KO	6.75±0.08	154±8

Supplemental Table 2. Standard deviation of NN intervals (SDNN), low frequency powers(LF), high frequency powers(HF), and the LF/HF ratio (sympathovagal balance) in male and female WT and ecCNP KO mice. n=11. *p<0.05, significantly different to female WT littermates.

Genotype	SDNN (ms)	LF (ms²)	HF (ms²)	LF/HF ratio
Male WT	6.99±0.18	11.01±1.09	11.75±0.67	0.86±0.07
Male ecCNP KO	7.88±0.26	14.17±1.81	19.27±3.27	0.91±0.19
Female WT	8.07±0.33	8.79±1.28	16.34±3.04	0.60±0.08
Female ecCNP KO	10.13±1.08	20.77±3.97*	19.54±2.54	1.14±0.16*

Supplemental Table 3. Venule diameter, centreline erythrocyte velocity, and wall shear rate of vessels explored in the intravital microscopy studies. n=5.

Genotype	Venule diameter (μm)	Centreline velocity (mm/s)	Wall shear rate (per s)
WT	25.8 \pm 0.8	2.06 \pm 0.07	391 \pm 45.9
ecCNP KO	22.9 \pm 2.2	1.97 \pm 0.06	394 \pm 42.0

Supplemental Table 4. Plasma lipid levels in WT and ecCNP KO mice. n=5.

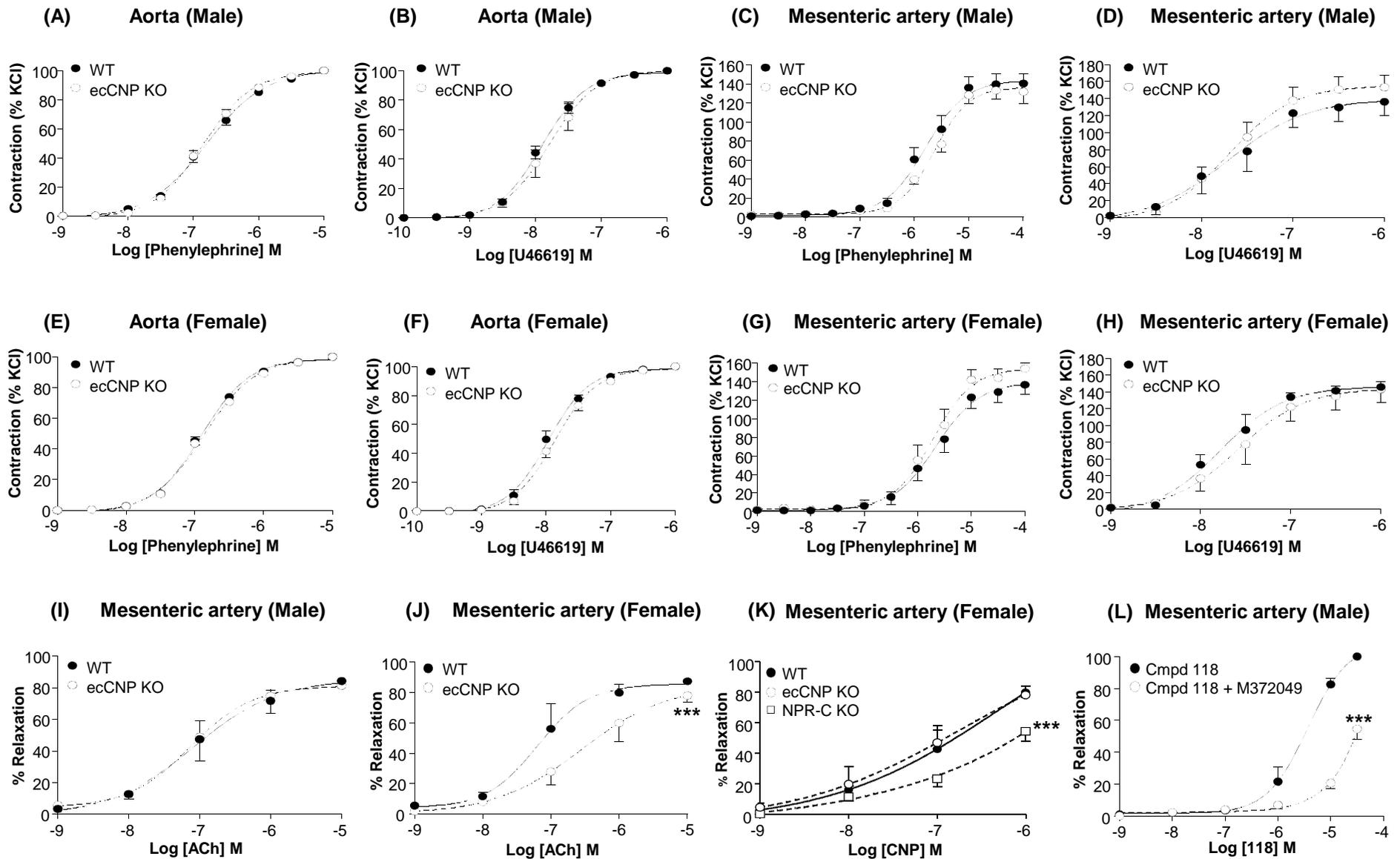
Genotype	<i>Total cholesterol (mg/dL)</i>	<i>HDL cholesterol (mg/dL)</i>	<i>LDL cholesterol (mg/dL)</i>
WT	361.6±32.3	23.1±3.5	338.4±30.7
ecCNP KO	297.6±34.0	27.0±5.7	270.6±32.6

Supplemental Table 5. Circulating cell populations (cells/uL) in whole blood from WT and ecCNP KO mice. n=5.

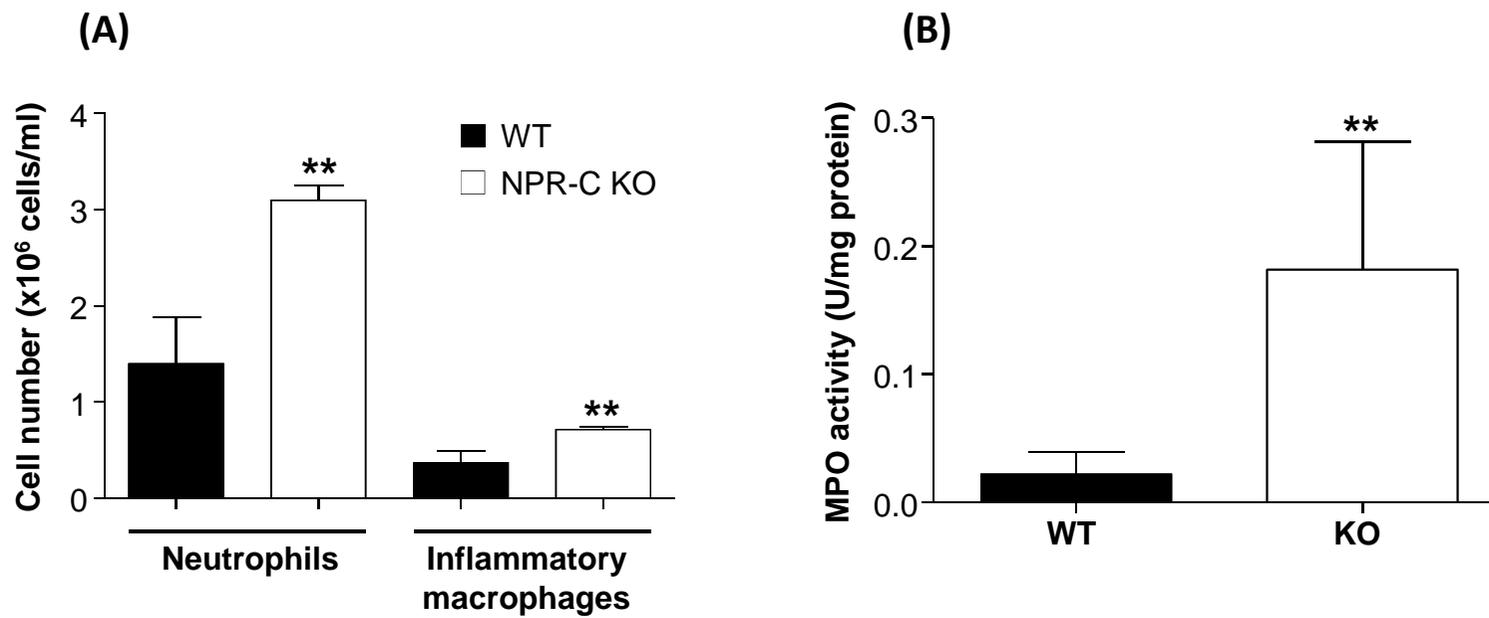
Genotype	Neutrophils	Monocytes	T-lymphocytes	B-lymphocytes	Platelets
WT	392.1±112.9	133.4±40.5	870.4±158.1	1742.0±332.8	1.21x10 ⁶ ±4983
ecCNP KO	359.6±41.2	117.7±32.6	1044.0±86.18	1921.0±421.7	1.11x10 ⁶ ±7511

Supplemental Table 6. Comparison of mean arterial blood pressure (MABP) in WT, ecCNP KO, and ecCNP/ApoE dKO mice. n=8 (WT & ecCNP KO) or n=3 (ecCNP/ApoE dKO). ***p<0.001, data significantly different to WT.

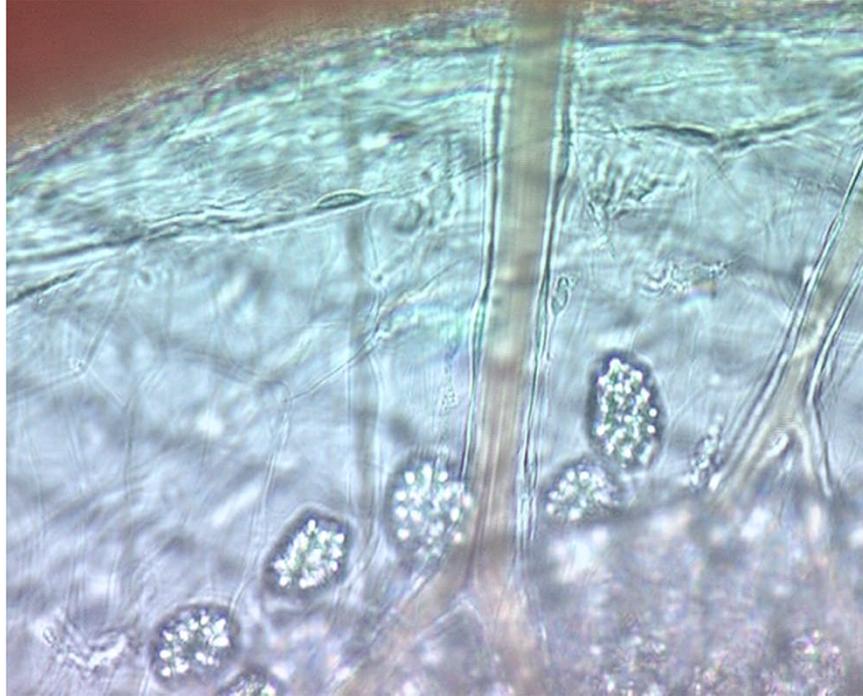
Sex	WT	ecCNP KO	ecCNP/ApoE dKO
Male	112.0±0.61	110.4±0.60	112.8±0.92
Female	105.3±0.56	117.0±0.82***	114.3±1.09***



Supplemental Figure 1. Vascular responses in ecCNP KO mice. Vasoconstrictor reactivity to the α_1 -adrenoceptor agonist phenylephrine and the thromboxane- A_2 mimetic U46619 in male (**A-D**) and female (**E-H**) aorta and mesenteric arteries was essentially identical in WT and ecCNP KO mice. Endothelium-dependent relaxation to acetylcholine (ACh) in the mesenteric artery of male ecCNP KO animals was unaltered in comparison to littermate controls (**I**). In contrast, there was a significant decrease in potency (rightward shift) of the concentration response curve to ACh in the mesenteric arteries of female ecCNP KO animals (**J**). The potency of CNP was not altered in WT versus ecCNP KO mouse mesenteric arteries, but blunted in NPR-C KO vessels (**K**). Responses to the novel NPR-C agonist compound 118 (**I**) were inhibited by the selective NPR-C antagonist M372049. Vasorelaxant responses in (**K**) and (**L**) were obtained in the presence of L-NAME and indomethacin. Data are represented as the mean \pm s.e.m. $n=6$ for the isolated vessel studies. *** $p<0.001$, significantly different to WT littermates (**J**) or absence of M372049 (**L**).



Supplemental Figure 2. Enhanced inflammatory response in ecCNP KO mice. Total cell number (**A**) and tissue MPO activity (**B**) in WT and ecCNP KO mice with TNF α -induced peritonitis. Data are represented as the mean \pm s.e.m. $n=4$. ** $p<0.01$ data significantly different to WT littermates.



Supplementary Video files. Leukocyte hyperreactivity in ecCNP KO mice. Representative intravital microscopy videos showing increased basal leukocyte rolling in ecCNP KO mouse post-capillary venules (*right panel*) as compared to WT littermates (*left panel*). Representative of at least 10 separate experiments.