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Propofol improves colonic but impairs hepatic mitochondrial function in tissue homogenates from healthy rats

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ABSTRACT

Evidence suggests that propofol infusion syndrome (PRIS) is caused by an altered mitochondrial function. The aim of this study was to examine the effects of propofol and the vehicle MCT on mitochondrial function in hepatic and colonic tissue.

Mitochondrial oxygen consumption was determined in colon and liver homogenates after incubation with buffer (control), propofol (50, 75, 100, 500 μM) or the carrier substances DMSO and MCT. State 2 (substrate-dependent) and state 3 (ADP-dependent respiration) were assessed. RCI (respiratory control index) - an indicator for coupling between electron transport chain system (ETS) and oxidative phosphorylation (OXPHOS) and ADP/O ratio - a parameter for efficacy of OXPHOS were calculated. Data were presented as % of control.

In hepatic mitochondria, 500 μM propofol reduced RCI formulation-independently (propofol/MCT 500 μM: complex I: 66.3 ± 8.7%*, complex II: 75.5 ± 9.2%*; propofol/DMSO 500 μM: complex I: 29.1 ± 8.8%*, complex II: 49.3 ± 15.5%*). 75 μM Propofol/MCT reduced ADP/O for complex I (73.5 ± 27.3%*). DMSO did not affect hepatic mitochondria whereas MCT reduced RCI for complex II (87.2 ± 9.8%*) and ADP/O for complex I (93.7 ± 31.7%*). In colon 50 μM Propofol/MCT increased RCI for complex I and II (complex I: 127.2 ± 10.7%*, complex II: 136.8 ± 33.9%*) and 100 μM Propofol/MCT for complex I (131.4 ± 18.7%*). 500 μM Propofol/DMSO increased ADP/O for complex I (139.4 ± 41.4%*). DMSO did not affect RCI but increased ADP/O for both complexes (complex I: 119.9 ± 25.8%*, complex II: 110.2 ± 14.2%*). MCT increased RCI for complex I (123.0 ± 31.6%*).

In hepatic mitochondria propofol uncoupled ETS from OXPHOS formulation-independently and propofol/MCT reduced efficacy of OXPHOS. In colonic mitochondria, propofol/MCT strengthened the coupling and propofol/DMSO enhanced the efficacy of OXPHOS.

1. Introduction

Propofol is a widely used drug for anaesthesia and sedation in intensive care units. Propofol infusion syndrome (PRIS) is a severe complication observed after prolonged or high-dose infusion of propofol. In the clinical setting propofol is used as an emulsion in a lipid containing solution. There are also reports on PRIS after a single application of propofol at a usual clinical dose (Michel-Macías et al., 2018). PRIS is characterized by either one or a combination of the following symptoms: unexplained metabolic acidosis, rhabdomyolysis, hyperkalemia, hepatomegaly, renal failure, hyperlipidemia, arrhythmia and rapid progressive cardiac failure (Krajčová et al., 2015). Since the 1980s it is assumed that PRIS is caused by an altered mitochondrial function (Krajčová et al., 2015). Many studies focussed on the influence of propofol on liver-, heart- and muscle mitochondria of rats, mice or rabbits after prolonged or high-dose propofol infusion (Vanlander et al., 2015)(Félix et al., 2017)(Campos et al., 2016). However, results from these studies are inconsistent: they showed either impaired or unaffected mitochondrial function. While there are plenty of studies on the influence of propofol dissolved either in a lipid (medium chain

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triglycerides - MCT) or dimethyl sulfoxide (DMSO) on hepatic and muscle mitochondria, no information exists on the role of propofol in conjunction with different solvent agents. Furthermore, there are no studies on the influence of propofol on colonic mitochondria.

The colon is an important organ being not only responsible for the resorbtion of water and nutrients but also serving as a container for the bacterial fermentation process. To prevent bacterial translocation and sepsis an undisturbed mucosal barrier function is not only essential under physiological but also under different pathological conditions. The barrier function can be easily disrupted by many determinants such as hypoperfusion of the gut, infections and toxins, but also selected overdosed nutrients or drugs and other lifestyle and environmental factors (Bischoff et al., 2014). Intact mitochondrial function is essential for barrier integrity. Uncoupling of oxidative phosphorylation (OXPHOS) in epithelial mitochondria results in decreased epithelial barrier function (Saxena et al., 2017)(Saxena et al., 2018).

The aim of this study was to examine the effects of propofol in different concentrations and the effect of the solvent per se on the mitochondrial oxygen consumption and the efficacy of the OXPHOS of the colon and the liver in vitro. To clarify this, three clinically achievable concentrations of propofol were chosen (50 µM ≙ 8.9 µg/ml, 75 µM ≙ 13.4 µg/ml, 100 µM ≙ 17.8 µg/ml) as they are found clinically in plasma during induction and maintenance of anaesthesia (Vanlander et al., 2015) (Branca et al., 1991) (Rigoulet et al., 1996). Furthermore, we tested one high propofol concentration (500 µM ≙ 89,18 µg/ml) (7) dissolved in either MCT (standard formulation clinically used) or DMSO. DMSO, as dissolvent, was chosen as alternative solvent agent for propofol, as it is one of the most known organic solvents used in the laboratory and it is supported by the literature that 1 vol% of DMSO has no effect on the respiratory chain in hepatic mitochondria (Syed et al., 2013).

2. Materials and methods

2.1. Animals

The study was approved from the Animal Ethics Committee of the University of Duesseldorf, Germany, and conducted in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. MaleWistar rats (3 months old, body weight 300 ± 35 g) were purchased from the breeding facilities of the University of Duuesseldorf (Germany) or from Janvier (France). They were kept at an artificial 12 h light/dark cycle at constant room temperature and humidity with free access to standard chow and tap water. Rats were sacrificed by decapitation under deep sedation with sodium pentobarbital (90 mg/kg) and afterwards the organs were harvested.

2.2. Preparation of liver and colon homogenates

Liver and colon homogenates were prepared as described previously (Herminghaus et al., 2019). Liver tissue was placed in 4°C-cold isolation buffer (130 mM KCl, 5 mM K_2HPO_4, 20 mM MOPS, 2.5 mM EGTA, 1 µM $Na_4P_2O_7$, 0.1% BSA pH 7.15), minced into 2–3-mm3 pieces, rinsed twice in isolation buffer to remove traces of blood, and homogenized (Potter-Elvehjem, 5 strokes, 2000 rpm). Freshly harvested colon tissue was placed in 4 °C-cold isolation buffer (as for the liver but cointaning 2% BSA), quickly opened, and dried softly with a cotton compress to remove remains of faeces and mucus. After treatment with 0.05% trypsin for 5 min on ice, the tissue was placed in 4 °C-cold isolation buffer containing 20 mg/ml bovine serum albumin (BSA) and protease inhibitors (cOmplete™ Protease Inhibitor Cocktail, Roche Life Science, Mannheim, Germany), minced into 2–3-mm^3 pieces, and homogenized (Potter-Elvehjem, 5 strokes, 2000 rpm). Protein concentration in the tissue homogenates was determined by the Lowry method (Lowry et al., 1951) with bovine serum albumin as a standard.

2.3. Measurement of mitochondrial respiratory rates

Mitochondrial oxygen consumption was measured as described previously (Herminghaus et al., 2019) (Herminghaus et al., 2018). Briefly, the measurement was performed at 30 °C using a Clark-type electrode (model 782, Strathkelvin instruments, Glasgow, Scotland). Tissue homogenates were suspended in respiration medium (130 mM KCl, 5 mM K_2HPO_4, 20 mM MOPS, 2.5 mM EGTA, 1 µM $Na_4P_2O_7$, 0.1% BSA for liver, and 2% BSA for colon, pH 7.15) to yield a protein concentration of 4 mg/ml or 6 mg/ml for liver and colon, respectively.

Mitochondrial state 2 respiration was recorded in the presence of either complex I substrates glutamate and malate (both 2.5 mM, G-M) or the complex II substrate succinate (10 mM for liver, 5 mM for colon, S) combined with rotenon - the inhibitor of complex I activity.

The maximal mitochondrial respiration in state 3 was measured after the addition of ADP (250 µM for liver, 125 µM for colon). The respiratory control index (RCI) was calculated (state 3/state 2) to define the coupling between the ETS and OXPHOS. To reflect the efficacy of OXPHOS, the ADP/O ratio was calculated from the amount of ADP added and oxygen consumption. The average oxygen consumption was calculated as the mean from three (liver) or two (colon) technical replicates.

The solubility of oxygen was assumed to be 223 µmol O_2/l at 30 °C according to the Strathkelvin instruments manual. Respiration rates were expressed as nanomoles per minute per milligramme protein. No correction of the natural drift of the electrode was made since a drift of less than 0.5% over 12 h is neglectable in our experimental setup.

Mitochondria were checked for leakage by the addition of 2.5 µM cytochrome *c* and 0.05 µg/ml oligomycin. There was no increase in flux after the addition of cytochrome *c*, indicating integrity of the mitochondrial outer membrane. When ATP synthesis was inhibited by oligomycin, the mitochondria were transferred to state 2, which reflects the respiration rate compensating the proton leak. The lack of difference in O_2 consumption after adding oligomycin compared to state 2 indicates that the inner membrane was intact and mitochondria were not damaged through the preparation procedure.

The resuspended homogenates were incubated in reaction tubes (Safe-Lock Tubes 1,5 ml, Eppendorf, Germany), with either no addition of substance (control), or 0.1% DMSO (or propofol/DMSO (50 µM, 75 µM, 100 µM or 500 µM propofol/0.1% DMSO)). The same experimental design was used for MCT: control (no additional substance), 0.1% MCT and propofol/MCT: propofol/MCT (50 µM, 75 µM, 100 µM or 500 µM propofol/0.1% MCT). The incubation took place at room temperature (kept at 21 °C) for 3 min 6 biological replicates and 2–3 technical were performed.

2.4. Statistical analysis

Statistical analysis was performed with GraphPad Prism 8.0 (GraphPad Software, Inc, La Jolla, USA). Tests for normality (Kolmogorov-Smirnov) showed a nonparametrically distributed data set. These non-parametric data were analysed utilising the Kruskal-Wallis test of variance followed by post-hoc Dunn's correction. Means ± standard deviations (S.D.) were determined. Data are presented as percentage of control values, $P < 0.05$ were considered significant.

3. Results

In hepatic mitochondria, MCT decreased the RCI for complex II (control 100%, MCT: 87.2 ± 9.8%, $P < 0.0001$) without affecting the RCI for complex I (Fig. 1). MCT decreased the ADP/O ratio only for complex I (93.7 ± 31.7%, $P = 0.0271$).

Propofol/MCT showed a reduction of RCI, but only at the highest concentration of 500 µM after stimulating the ETS through both complexes (control: 100%, propofol/MCT 500 µM for complex I:

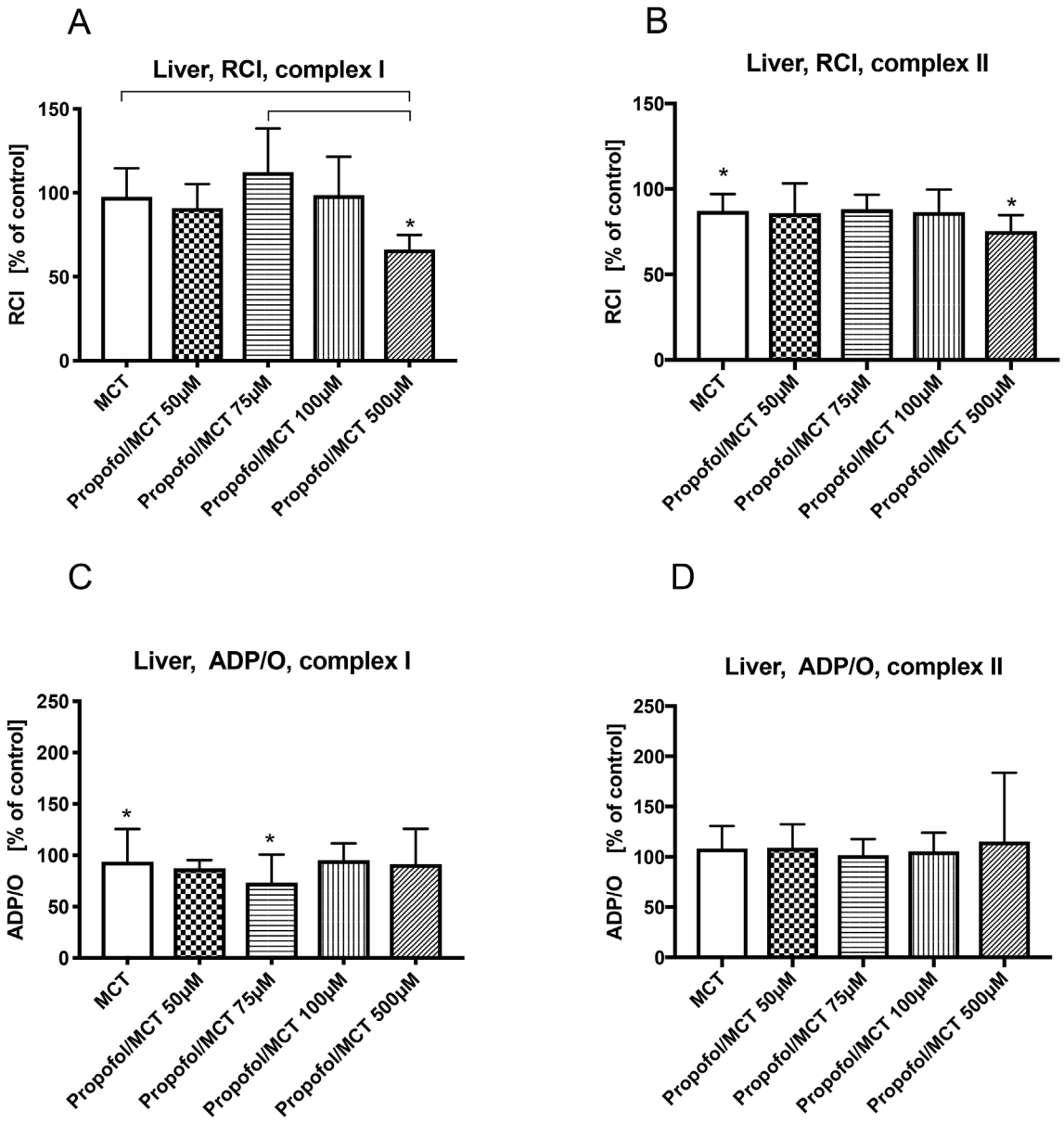

Fig. 1. Influence of MCT and propofol/MCT in different concentrations (50 µM, 75 µM, 100 µM and 500 µM) on RCI after stimulation through complex I (A) and complex II (B) and ADP/O ratio (C, D) on liver homogenate. Data are presented as mean ± S.D., n = 6, *P < 0.05 vs. control, P < 0.05 between groups.

66.3 ± 8.7%, P = 0.0003, propofol/MCT 500 µM for complex II: 75.6 ± 9.2%, P < 0.0001) and decreased the ADP/O ratio for complex I at a concentration of 75 µM (73.5 ± 27.3%, P = 0.0271) (Fig. 1).

DMSO did not show any effect, neither on RCI nor on the ADP/O ratio in hepatic mitochondria (Fig. 2).

Propofol/DMSO decreased the RCI for complex I at 500 µM (control: 100%, propofol/DMSO 500 µM: 29.1 ± 8.8%, P = 0.0008) and for complex II in almost all concentrations (control: 100%, propofol/DMSO 50 µM: 85.3 ± 6.9%, P = 0.0117, propofol/DMSO 100 µM: 89.3 ± 6.0%, P = 0.0448, propofol/DMSO 500 µM: 49.3 ± 15.5%, P < 0.0001). Propofol/DMSO had no effect on the ADP/O ratio (Fig. 2).

In colonic mitochondria, MCT increased the RCI for complex I compared to the control (control: 100%, MCT: 123.0 ± 31.6%. P = 0.007), but caused no alteration in the ADP/O ratio for both complexes (Fig. 3).

Propofol suspended in MCT also increased the RCI, but predominantly in low concentrations (complex I: control: 100%, propofol/MCT 50 µM: 127.2 ± 10.7%, P = 0.006, propofol/MCT 100 µM: 131.4 ± 18.7%, P = 0.0043, complex II: control 100%, propofol/MCT 50 µM: 136.8 ± 33.9%, P = 0.0065) (Fig. 3). A trend towards an increased RCI could also be observed for the concentration of 100 µM at complex II, but with no significance (126.7 ± 32.1%, P = 0.0532). No significant changes could be registered for the ADP/O ratio of complex I and II compared to the control (Fig. 3).

DMSO did not change the RCI, but significantly increased ADP/O ratio for both complexes in colonic mitochondria compared to control (complex I: control 100%, DMSO 119.9 ± 25.8%, P = 0.0019, complex II: control 100%, DMSO: 110.2 ± 14.2%, P = 0.0046) (Fig. 4).

Propofol solved in DMSO in different concentrations showed no significant alteration of mitochondrial function, except of 500 µM propofol, which increased the ADP/O ratio in complex I (139.4 ± 41.4%, P = 0.0026), leaving the RCI unaltered (Fig. 4).

4. Discussion

The main result of this study is that the effect of the solvent agent

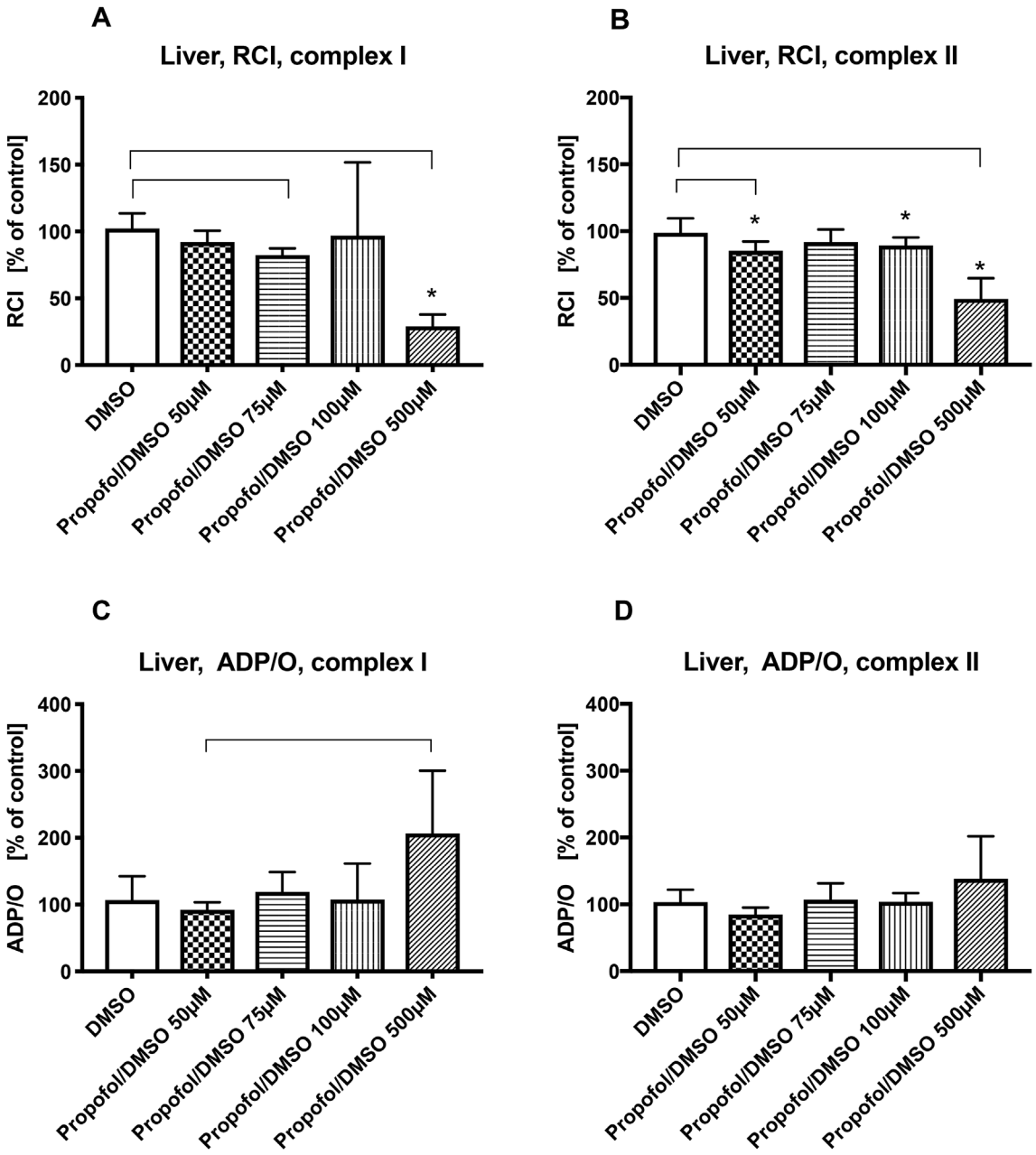

Fig. 2. Influence of DMSO and propofol/DMSO in different concentrations (50 µm, 75 µM, 100 µM and 500 µM) on RCI after stimulation through complex I (A) and complex II (B) and ADP/O ratio (C, D) on liver homogenate. Data are presented as mean ± S.D., n = 6, Kruskal-Wallis + Dunn's correction, *P < 0.05 vs. control, P < 0.05 between groups.

MCT and of the acting agent propofol is organ specific. In hepatic mitochondria propofol uncoupled ETS from OXPHOS formulation independently and reduced efficacy of OXPHOS when suspended in MCT. In colonic mitochondria, propofol/MCT enhanced the electron coupling and propofol/DMSO enhanced the efficacy of OXPHOS.

For our experiments we chose three clinically achievable concentrations of propofol (50 µM ≙ 8.9 µg/ml, 75 µM ≙ 13.4 µg/ml, 100 µM ≙ 17.8 µg/ml) and one high concentration (500 µM ≙ 89,18 µg/ml). The highest concentration of 500 µM were chosen based on studies performed in vitro with rat tissues (Vanlander et al., 2015) (Rigoulet et al., 1996). Vanlander at al. saw the effects of propofol by in vitro experiments only using high concentrations (200–400 µM). By in vivo experiments, the effect could be shown already by 20 µM. The authors suggests that the discrepancy between the results of the in vivo and in vitro experiments can be explained by a different incubation time of propofol and its different distribution between aqueous and membrane phase.

In hepatic mitochondria, MCT had no effect on the RCI of complex I, but decreased the efficacy of the OXPHOS as indicated by a significantly decreased ADP/O ratio. In contrast, the RCI of complex II was significantly decreased, but no alteration of the ADP/O ratio was observed. Campos et al. (2016) found that lipid emulsions (SMOFlipid 20%, Fresenius Kabi, Sweden) may decrease ADP-dependent respiratory rate for complex II. The decreased state 3 for complex II is in line with the findings of this study. We show a decreased RCI which is caused by a decreased state 3 and increased state 2 (data not shown). From earlier studies it is known that MCT has a “pseudouncoupling effect” (Schönfeld and Wojtczak, 2016) on liver mitochondria in complex I and II. This is reflected in a decreased electron coupling and increased oxygen consumption.

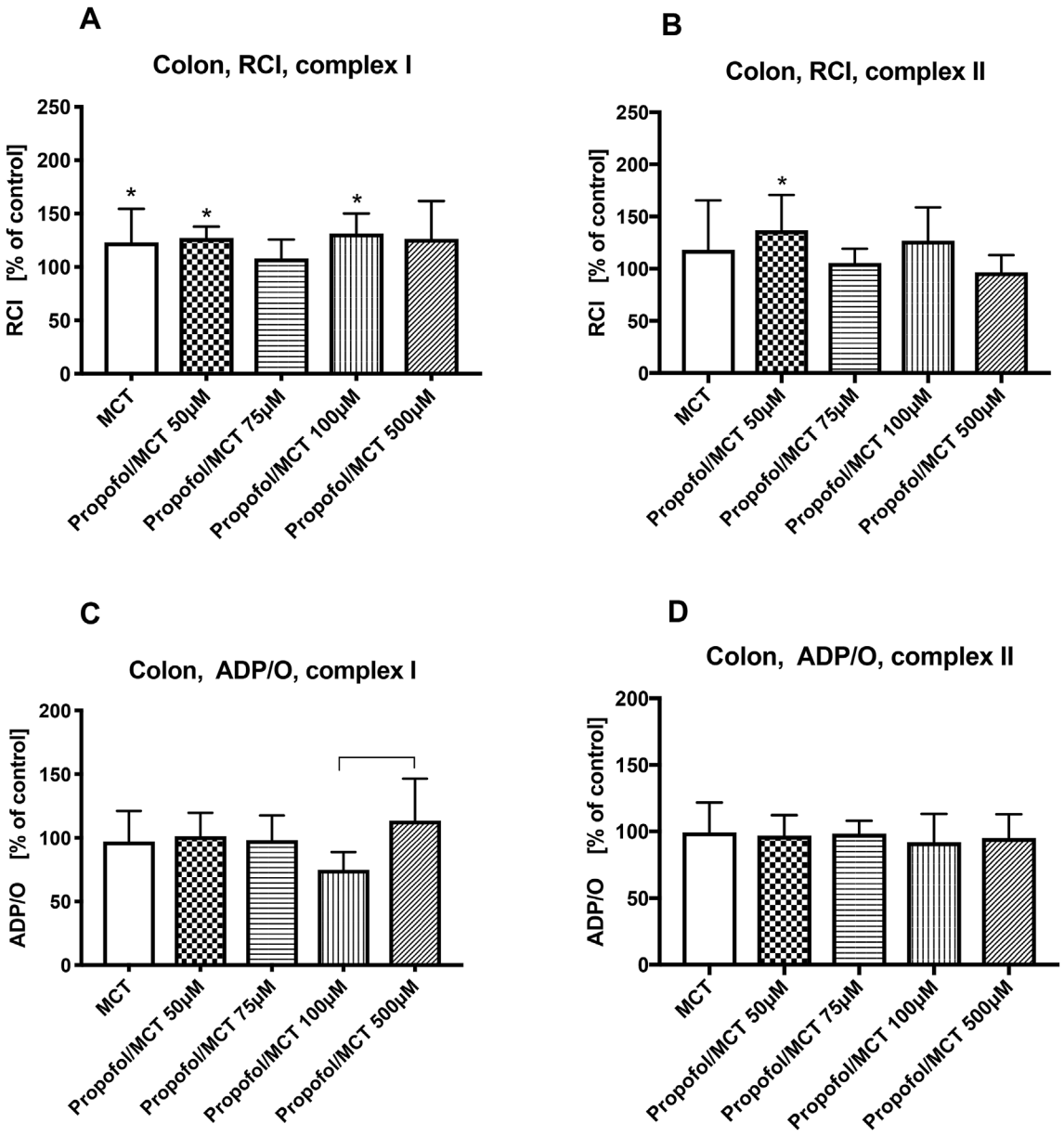

Fig. 3. Influence of MCT and propofol/MCT in different concentrations (50 µm, 75 µM, 100 µM and 500 µM) on RCI after stimulation through complex I (A) and complex II (B) and ADP/O ratio (C, D) on colon homogenate. Data are presented as mean ± S.D., n = 6, Kruskal-Wallis + Dunn's correction, *P < 0.05vs. control, P < 0.05 between groups.

Medium chain fatty acids are activated to their CoA thioesters in the mitochondrial matrix compartment. This process utilizes ATP and releases AMP and pyrophosphate (PPi). AMP can subsequently react with ATP yielding two molecules of ADP that are rephosphorylated at the expense of the mitochondrial transmembrane potential, thus producing an uncoupling-like effect. In addition, both acyl- AMP and acyl-CoA are subject to slow hydrolysis, thus increasing AMP production and futile energy utilization (Schönfeld and Wojtczak, 2016)(Nobes et al., 1990) (Plomp et al., 1985).

Our data support the pseudo-uncoupling effect only for complex II and a significantly increased oxygen consumption was only recorded for complex I. Even though, studies found the pseudo-uncoupling effect and the increased oxygen consumption at various concentrations of single compounds of MCT with different effects-sizes depending on the buffer medium (Schönfeld and Wojtczak, 2016). The formulation of MCT used in this study was probably differently balanced, as the exact composition of LipovenösMCT 20% is not provided.

Propofol/MCT showed an uncoupling effect on hepatic mitochondria only at the 500 µM concentration after stimulation of the ETS through both complexes. Rigoulet et al. (1996) showed similar results at propofol concentrations of 400 µM decreasing the respiratory rate significantly, with only slightly affected ADP/O ratio. The efficacy of the OXPHOS was significantly decreased only for complex I at the 75 µM concentration. This result indicates that propofol and MCT might have additive effects. Nevertheless, this effect was only observed at the medium concentration of 75 µM propofol/MCT – neither 50 µM, nor 100 µM/500 µM influenced the efficacy of OXPHOS. It seems that propofol at a high concentration acts synergistically amplifying the pseudo uncoupling effect of MCT. This is supported by the fact, that propofol/DMSO does not affect the ADP/O ratio.

In contrast to MCT, DMSO, used as solvent for the pure substance propofol, did not affect parameters of mitochondrial function in liver homogenate.

This finding is well supported by the literature (Syed et al., 2013).

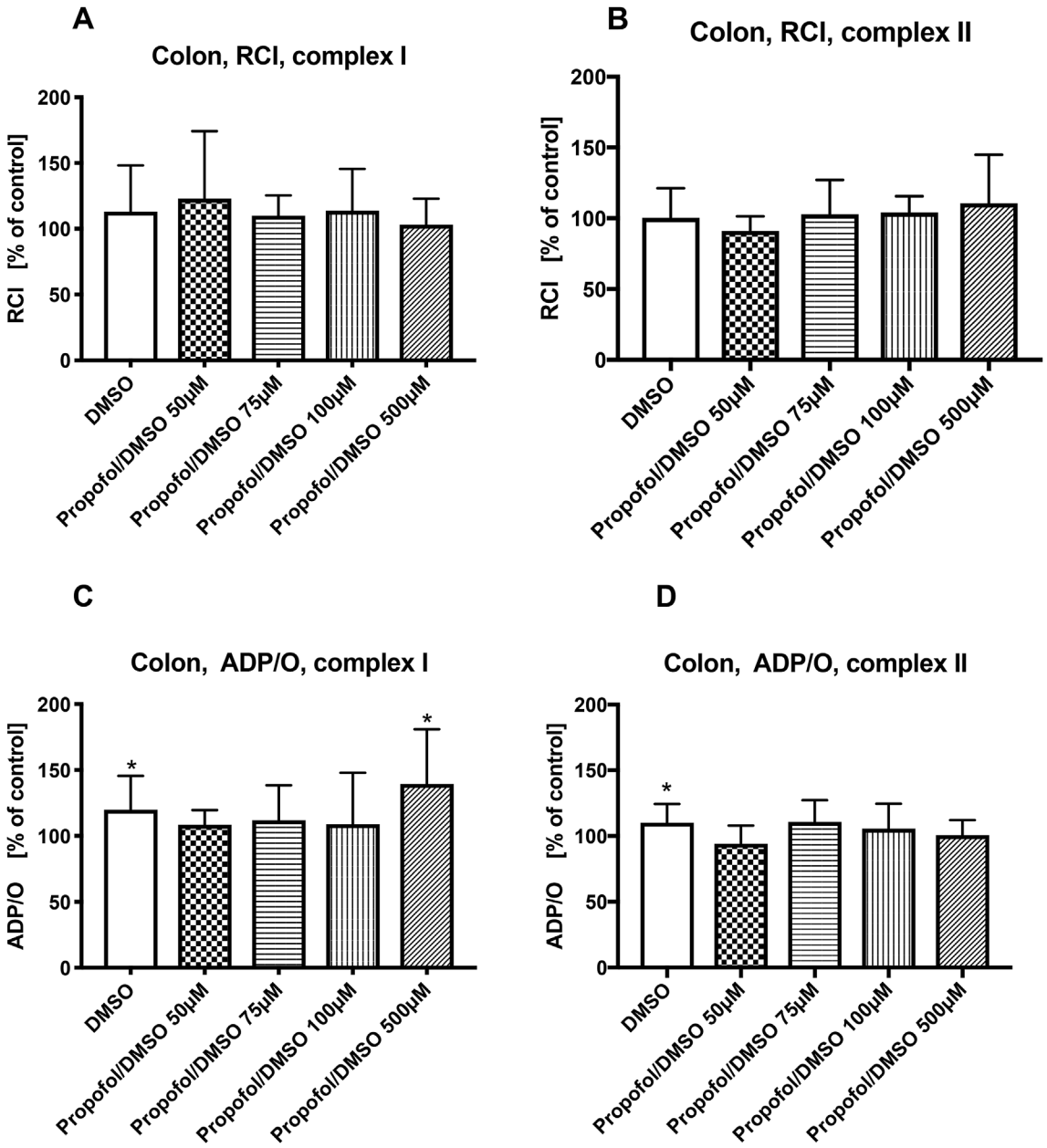

Fig. 4. Influence of DMSO and propofol/DMSO in different concentrations (50 µm, 75 µM, 100 µM and 500 µM) on RCI after stimulation through complex I (A) and complex II (B) and ADP/O ratio (C, D) on colon homogenate. Data are presented as mean ± S.D., n = 6, Kruskal-Wallis + Dunn's correction, *P < 0.05 vs. control, P < 0.05 between groups.

The high concentration of 500 µM propofol in DMSO led to uncoupling, which can be attributed solely to the influence of propofol. This effect can potentially be credited to the interactions of propofol with the mitochondrial membrane potential and complex activities located in deeper regions of the bilayer especially of complex II (Félix et al., 2017). A high but not significantly increased ADP/O ratio by 500 µM propofol is probably caused by reduced oxygen consumption by terminal uncoupling.

Results for colonic mitochondria were different. Mitochondrial function was rather positively affected by MCT and propofol. In detail, colonic mitochondria showed an increased RCI for complex I in the presence of MCT. ADP/O ratio for complex I remained unchanged after incubation with MCT. Both parameters – RCI and ADP/O ratio – for complex II were not affected by MCT. In colonic mitochondria, propofol/MCT significantly improved the ETS reflected by the increased RCI, especially at low concentrations (50 µM and 100 µM for complex I and 50 µM for complex II). However, these results were not significantly different compared to MCT only. This finding indicates that propofol has additive effects to MCT. However, it cannot be excluded, that the observed effects of propofol/MCT are predominantly caused by MCT. No effect on the ADP/O ratio after stimulating complex I or II was shown neither in the presence of MCT nor in the presence of propofol/MCT. From these results it can be concluded that neither MCT nor propofol/MCT have a negative impact on parameters of mitochondrial function in colon homogenates.

DMSO showed also different results in colon homogenates compared to liver homogenates.

DMSO had no effect on the electron coupling on colon homogenates, but improved significantly the efficacy of OXPHOS in both complexes. 500 µM propofol/DMSO only increased the ADP/O ratio when complex I substrate was present, increasing the ADP/O ratio by a factor of 1.4. As DMSO already amplified the ADP/O ratio, it could be assumed that

propofol acted synergistically to DMSO, thereby further increasing the efficacy of the OXPHOS in complex I. Another explanation could be that propofol in low concentrations rather decreased the efficacy of OXPHOS and diminished the amplifying effect of DMSO. To our best knowledge, there is no data about the influence of propofol on colonic mitochondrial function, so no comparison with other results can be made.

5. Conclusions

Propofol/MCT exhibits organ specific effects on the mitochondrial oxygen consumption. In high concentrations propofol/MCT demonstrates an uncoupling effect on hepatic mitochondrial respiration, with a reduction of the efficacy of OXPHOS, probably caused by MCT. This may be important as propofol is clinically only used as a fat emulsion. Colon seems to be more resistant against the effects of the clinically used propofol/MCT formulation. Propofol/MCT rather improves the coupling of the ETS and the ATP synthase, without effects on the efficacy of the OXPHOS.

Studies suggest that PRIS is mainly caused by propofol-induced alterations in mitochondrial function. Findings from this study provide evidence that the active drug propofol might not be the only factor reducing mitochondrial function in the liver; rather, the clinically used fat formulation seems to synergistically reduce the efficacy of the OXPHOS. This could at least partially explain the clinical manifestation of liver insufficiency in PRIS. To confirm this hypothesis further research is needed. One should consider, that PRIS is a very complex process. Biochemical changes caused by propofol are only one of many factors playing a role in pathogenesis of PRIS. Any other aspects, like patient state or other pharmacological agents are not considered in this study.

In contrast, propofol/MCT seems to have a rather positive effect on the colon. To explain the mechanisms behind this phenomenon further research is needed.

Authors' contributions

AH and JB contributed equally to the mansucript and are responsible for the conception and design, the acquisition of data, analysis and interpretation of data, and drafting the article, CV, JS, IB and OP are responsible for the analysis and interpretation of data and revising the article. . RT is responsible for the analysis and interpretation of data, and revising the article. All authors read and approved the final manuscript.

Conflicts of interest

The authors declare that they have no competing interests. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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