O2k brief Toxicology
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High-resolution respirometry: Toxicology

Cell-Permeable Succinate Rescues Mitochondrial Respiration in Cellular Models of Statin Toxicity

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Statin concentration-dependent effects on mitochondrial respiration

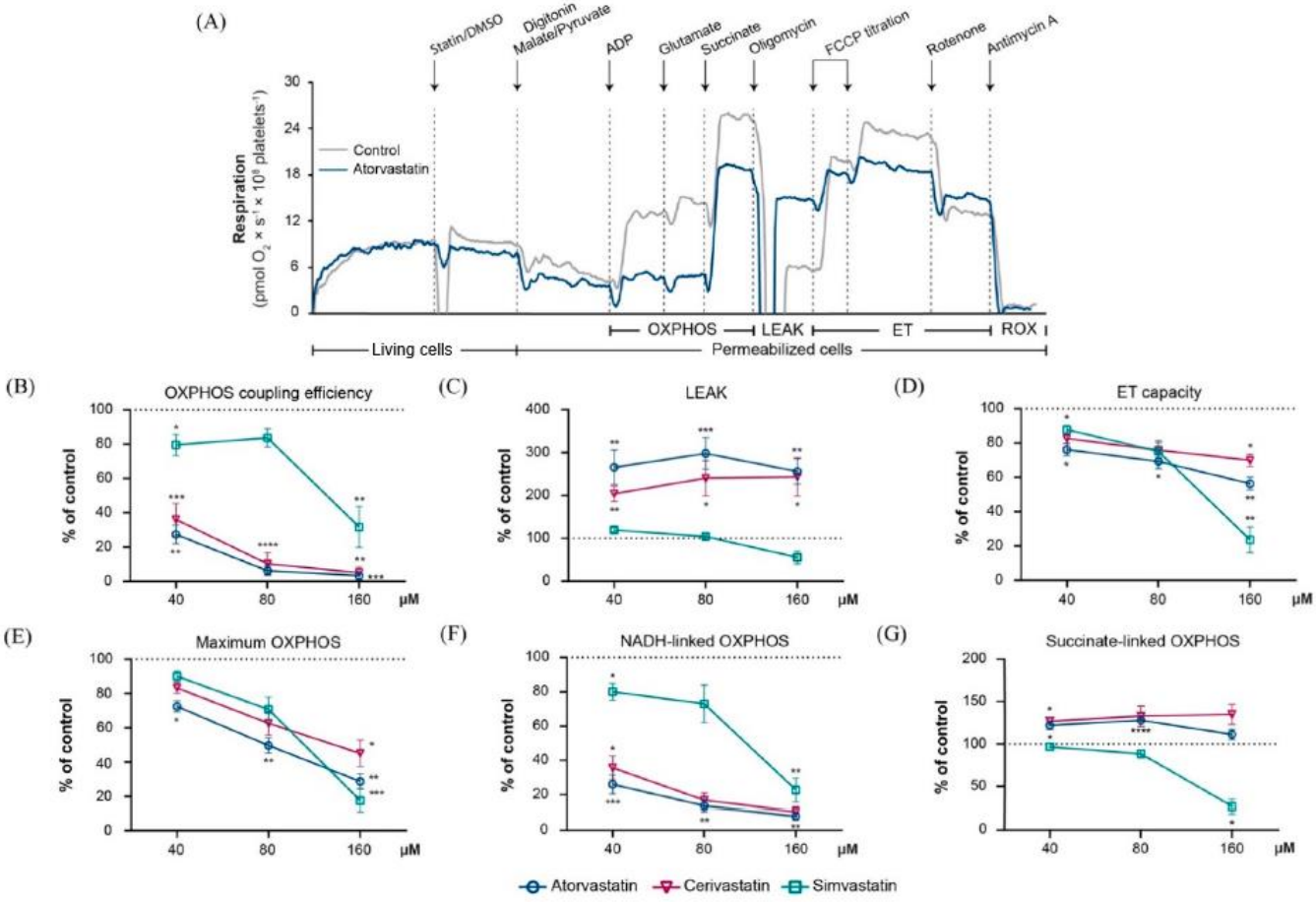

Figure 1. Statins induced a concentration-dependent effect on mitochondrial respiration in permeabilized human platelets. **(A)** Representative traces of atorvastatin 40 μM (blue) and DMSO (grey). Concentration-dependent effects were assessed for 3 concentrations (40 μM, 80 μM and 160 μM, respectively) of atorvastatin (blue open circle), cerivastatin (pink open triangle) and simvastatin (turquoise open square), respectively. OXPHOS coupling efficiency **(B)**, LEAK **(C)**, maximal ET **(D)**, maximum OXPHOS **(E)**, NADH-linked OXPHOS **(F)**, and succinate-linked OXPHOS **(G)** capacities were evaluated. Data is expressed as mean ± SEM of the percent of control (platelets exposed to the corresponding volume of DMSO for each of the 3 concentrations of statin). Two-way ANOVA with Bonferroni post hoc test was performed on antimycin-corrected data. DMSO, dimethyl sulfoxide; ET, electron transport; LEAK, non-phosphorylating resting state; OXPHOS, oxidative phosphorylation; ROX, residual oxygen consumption. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ vs. DMSO.

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Effects of cell permeable succinate prodrug NV118 on statin-dependent respiratory dysfunction in human platelets

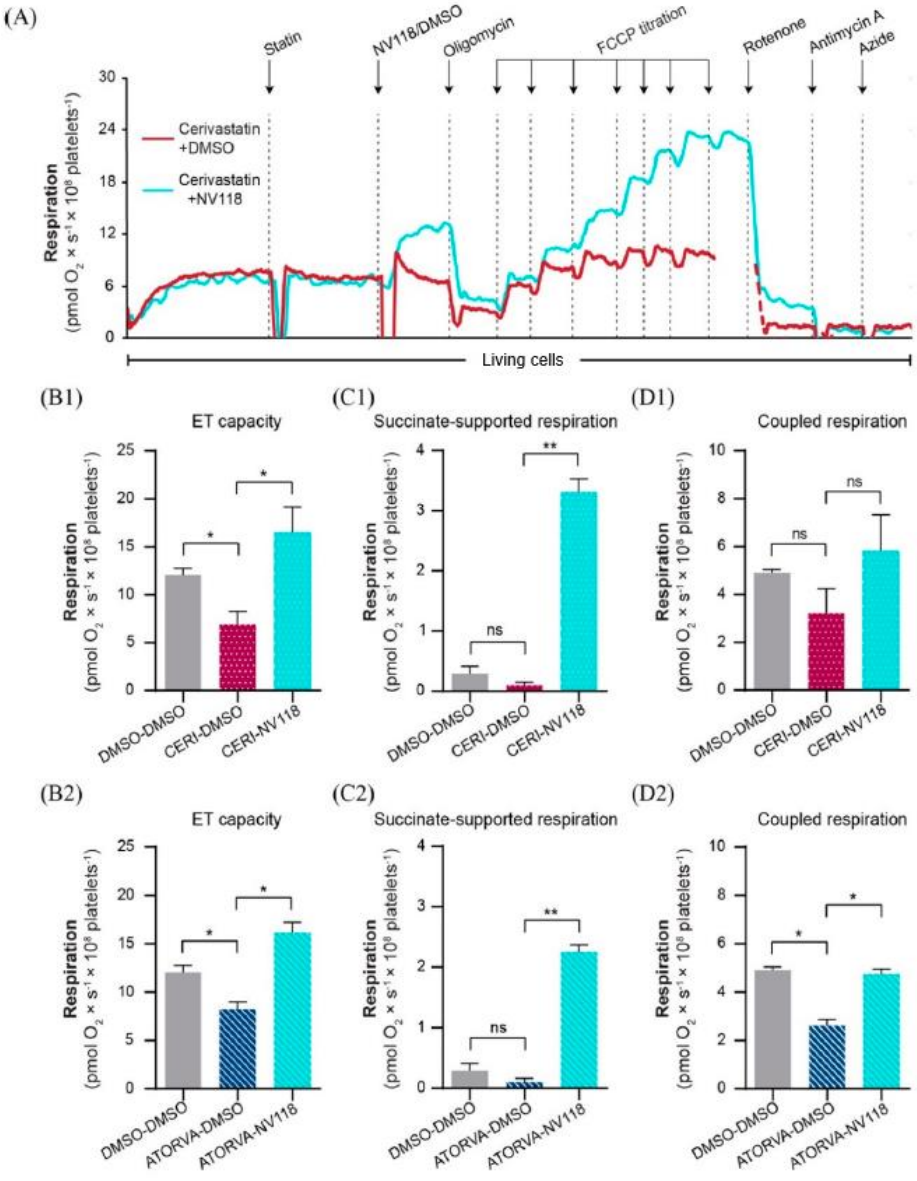

Figure 2. (A) Representative overlay trace of statin-exposed platelets in the absence (red) or presence (blue) of the succinate prodrug NV118. NV118 effects in cerivastatin (80 µM) **(B1**, **C1**, **D1)** and atorvastatin (80 µM) **(B2**, **C2**, **D2)** exposed platelets were measured as compared to its vehicle (DMSO). As negative control of the experiment, platelets were exposed only to DMSO (DMSO-DMSO). Data is expressed as mean ± SEM. One-way ANOVA with Bonferroni post hoc test was performed on antimycin-corrected data. ATORVA, atorvastatin; CERI, cerivastatin; DMSO, dimethyl sulfoxide; ET, electron transport. ns = no significance; * $p < 0.05$; ** $p < 0.01$.

Statins decrease mitochondrial respiration by inhibiting NADH-linked respiration. Cell-permeable succinate can restore mitochondrial respiration by stimulation of succinate-linked respiration.

Reference: Avram VF, Chamkha I, Åsander-Frostner E, Ehinger JK, Timar RZ, Hansson MJ, Muntean DM, Elmér E (2021) Cell-permeable succinate rescues mitochondrial respiration in cellular models of statin toxicity. Int J Mol Sci 22:424

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