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Rationale: Chemotherapy-induced cachexia is a syndrome of uncontrolled muscle loss that exacerbates cancer-related cachexia. Although skeletal muscle mass is predictive of long-term survival, there are currently no defined therapeutic strategies to counteract this muscle wasting. We previously demonstrated that cannabidiol (CBD) can prevent cell death, muscle atrophy and mitochondrial alterations *in vitro* in response to cisplatin treatment[1]. The aim of this study was to evaluate whether the documented effects of CBD could be different depending on the type of chemotherapy used.

Methods: After differentiation, C2C12 cells (a model of myotubes) were incubated in the presence of 10-50µM cisplatin or 5-20µM oxaliplatin (chemotherapy) for 48 hours with or without CBD (5µM). Myotube diameter was analyzed by microscopy. The activation of the mTOR pathway (phosphorylation state of Akt and S6K1), the levels of cleaved-caspase3, the protein expression of the different respiratory complexes (OXPHOS), and markers of mitochondrial dynamic (MFN2, OPA1, DRP1,Parkin) were analyzed by western blot. Results were analyzed by two-way ANOVA and expressed as mean ± sem.

Results: Cisplatin and oxaliplatin treatments decreased the rate of Akt and S6K1 phosphorylation and myotube diameters (-25 and -30%, respectively, $p<0.01$) ; the later being associated with increased levels of cleaved-caspase 3 (index of apoptosis). CBD prevented atrophy of myotubes only after treatment with cisplatin. It restored the phosphorylation level of Akt and S6K1 and prevented the induction of apoptosis in cisplatin. With oxaliplatin, CBD only prevented the decreased S6K1 phosphorylation. Both cisplatin and oxaliplatin induced an increased protein expression of NDUFB8 (markers of mitochondrial complex I, +104% and +100% $p<0.01$, respectively), which was reduced by CBD ($p<0.05$) in both conditions. Protein expression of parkin (marker of mitophagy), was increased 4- and 6-times in response to oxaliplatin and cisplatin, respectively ($p<0.05$), and was decreased in response to CBD only after cisplatin treatment ($p<0.05$).

Conclusion: These results show that, in a model of myotubes in culture, CBD can prevent muscle atrophy, cell death, and mitochondrial alterations that are associated with chemotherapy. This suggests that CBD could be used in the treatment of cancer cachexia to help maintain muscle mass. However, CBD effects seem to depend on the chemotherapy used.

Conflicts of interest: No conflicts to declare.

1. Le Bacquer O, Sanchez P, Patrac V, Rivoirard C, Saroul N, Giraudet C, Kocer A, Walrand S. Cannabidiol protects C2C12 myotubes against cisplatin-induced atrophy by regulating oxidative stress. Am J Physiol Cell Physiol 2024 Apr 1;326(4):C1226-C1236.