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Mitochondrial metabolites acylcarnitines: therapeutic potential and drug targets

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Manuscript reviewed 2022-07-03 (round 1) 2022-09-24 (round 2): *Only major points included.*

Round 1

Reviewer 2

This is a short revision paper that puts in perspective the potential role of long known acylcarnitines as metabolites of fatty acid and amino acid metabolism that have been used for decades as biomarkers for not only inherited diseases related with energy metabolism as well as more recently also of common and acquired diseases affecting directly and indirectly energy metabolism and cell homeostasis such as diabetes, heart conditions, neurological disorders and in some cancers as well as drug-induced mitochondrial dysfunction. This is not a new subject but it is still highly relevant to the understanding, the diagnosis and the management of these diseases as demonstrated by the increasing number of related publications over the years including recent publications. The interesting aspect of this publication is the mention of potential role of not only elevated but also of decreased levels of acylcarnitine in some disorders apparently not related with energy metabolism such as central nervous system diseases, namely Alzheimer's and schizophrenia, and some types of cancer, as breast and hepatocellular carcinoma. This is a different look into the levels of acylcarnitines in the body and their meaning as well a look for compounds that may decrease bodies' acylcarnitine levels in case of disease. Further knowledge in the role of already approved drugs upon acylcarnitine profiling is of extreme importance specially in the case of inherited metabolic diseases with energy deficit where acylcarnitines of different chain-lengths may pile up and compromise other function in the body. These disorders although known for so long have still no pharmacology options for treatment except the use of supplements such as L-carnitine that in many cases only increase the problem with the production of more acylcarnitines that will further affect mitochondrial and cell functions. Due to the high cost of drug development, repurposing of a previously approved drugs for a different indication, specially if this is a condition with an unmet medical need, is currently of high interest as an option to make accessible faster and at a lower cost new therapeutic strategies to some diseases In fact, drug repurposing is currently the subject of incentives to original drug owners or other developers (in case patents are no longer a limitation) to further explore approved drugs in different disease settings. Despite of the

interest of the aspects raised in the paper, for which the authors are appraised, the fact is that every aspect is only high level addressed and the new points of view, the new strategies that have not been covered already in the recent review published by some of the authors (Dambrova M) are only briefly included herein. Even so, some suggestions for improvement are included as comments below (as well as in the document uploaded).

Authors

We thank the Reviewer for comments and suggestions. We believe that more data should be collected to draw more solid conclusions about different roles of acylcarnitines as well usefulness of targeting acylcarnitines (level regulation) by drugs. The mentioned recent review (Dambrova et al, PharmRev 2022) covers the acylcarnitine-related nomenclature, biochemistry and disease/condition information and clinical trial data. Here we want to introduce readers to acylcarnitine field and provide an insight about effects of known drugs on acylcarnitine levels. We hope that this will raise interest in acylcarnitine topic in future. We agree and accepted all changes in the text suggested by the reviewer.

Reviewer 2

The abstract calls the attention to the interest and relevance of acylcarnitines and in particular long-chain acylcarnitines as biomarkers of diseases primarily or secondarily affecting or changing energy metabolism and of their use in measuring the efficacy/effectiveness of potential drugs targeting those clinical conditions. However, it should be more open to the new aspects of the information collected and on the conclusion that can be drawn from it. In order words, it raises the interest of the reader but then does not go further. If the aim of the authors is leading the reader to the read of the entire paper they are successful. Nevertheless, it would be improved if made more specific and to the point.

Authors

We thank the reviewer for interest in the acylcarnitine topic and we are sorry that at the moment the conclusions are not "to the point". More comprehensive analysis of drug effects on acylcarnitine levels (especially aiming at repurposing) will be possible in some year time when ongoing metabolomic studies will be finalized and results (especially from clinical trials) published.

Reviewer 2

Introduction - Referring to acylcarnitines as "emerging" important fatty acid metabolites and biomarkers for the diagnosis of inherited diseases of fatty acid metabolism is not correct. The importance of these metabolites of fatty acid metabolites and their use as biomarkers for the diagnosis for fatty acid metabolism disorders is recognized since at least the 80s from the XXth century (e.g, Review paper in DOI: 10.1007/BF01812855). In fact the authors themselves in the reference "Dambrova M 2022" refers as well " They have historically been used as important diagnostic markers for inborn errors of fatty acid oxidation". You could say they are emerging biomarkers for insulin resistance and heart failure though however the same review from Dambrova M 2022 refers to publication from 2009 in this respect and goes even back in time while citing "The first review in the area of acylcarnitines was published in 1975 with a primary

focus on the role of acylcarnitines in fatty acid oxidation arising from ischemia (Hull et al., 1975". So, proposed to delete the word "emerging" as it is misleading to a novel issue which is not the case.

Authors

Thank you for noticing this. We agree and accepted the change in the text suggested by the reviewer.

Reviewer 2

Table 2 - An additional column with the effect on the acylcarnitine levels (increase/decrease) from the use of each drug would be of interest and would allow to substantiate the proposal for repurposing mentioned below.

Give examples. The examples given above are from drugs that induce the increase of acylcarnitine levels and only meldonium is mentioned as potential useful to reduce the levels of acylcarnitines.

Authors

A new column (Effect on plasma acylcarnitines, sample origin) is added to the Table 2 as suggested by the reviewer.

As now seen in Table 2, meldonium and also liraglutide, atorvastatin, rouvastatin have been shown to reduce levels of some long-chain acylcarnitines. The respective sentence is changed to: In conclusion, some clinically approved cardiovascular and diabetes drugs (Table 2) have been shown to reduce long-chain acylcarnitine concentrations in vivo....

Round 2

Reviewer 2

This is a resubmission of a short revision paper that was previously peer-reviewed and considered still not adequate for publication. The authors have agreed with the reviewers' suggestions and updated the paper accordingly. Of particular importance are the changes introduced to Table 2 which is now much more informative and relevant for the aim of the paper and the conclusion drawn. The changes introduced in the updated version improved the paper quality and considering this is a revision paper it can now be recommended for publication. Even so, it is still suggested that the abstract should be revised and before the final paragraph a brief reference should at least be included regarding the most important data collected in the paper: the impact of some approved drugs in the acylcarnitine levels and the need to explore their potential repurpose for the treatment of diseases primarily or secondarily related with mitochondrial energy metabolism deficiency.

Authors

We thank the Reviewer for comments and suggestions. Now, we have modified the last sentence in the Abstract and added sentence in the last paragraph of Discussion, as suggested by the Reviewer:

Abstract -A better understanding of biochemical and molecular mechanisms behind the changes in acylcarnitine levels and their physiological and pathological roles forms the basis for future therapeutic target selection and preclinical drug discovery, as well as explains off-target effects of some clinically used drugs that might point to new indications for repurposing.

Discussion (lines 158-160) - Currently, insulin and GLP-1 agonists are the most promising repurposing candidates for the treatment of diseases primarily or secondarily related to mitochondrial energy metabolism deficiency.