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Commentary

Considerations for exerkine research focusing on the response to exercise training

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García-Hermoso and colleagues[1] recently published a systematic literature review and meta-analysis on exercise training-induced changes in exerkine concentrations in type 2 diabetes mellitus patients, providing a contemporary view on how exerkines respond to exercise training. That review prompted us to highlight 2 additional considerations that should be taken into account when studying the response of exerkines to exercise training. Firstly, whether exerkines can exhibit discordant responses to acute exercise compared to exercise training, and secondly, the need to consider the residual effects of the most recent exercise bout.

The term "exerkine" has been operationally defined as "a signaling moiety released in response to acute exercise and/or chronic exercise, exerting its effects through endocrine, paracrine, and/or autocrine pathways", and encompasses "a broad range of signaling moieties, including cytokines, nucleic acids (microRNA, mRNA, and mitochondrial DNA), lipids, and metabolites, which are frequently driven by cell-specific extracellular vesicle secretion".[2] To date, most exerkine research has focused on molecules that have circulating concentrations that are increased in response to acute exercise.[2,3] Whether there are changes in resting concentrations of exerkines as a consequence of exercise training is an important question for the field. For example, health benefits conveyed by exerkines may be limited to the effects of acute exercise whereby exerkines function through stimulating transient changes in tissue metabolism via signal transduction and/or altered gene expression. Alternatively, exerkines could play a more comprehensive role in conveying the benefits of exercise whereby exercise training induces altered exerkine profiles at rest that lead to more persistent changes in tissue metabolism and/or signaling, thereby creating a more prolonged time course of benefit.[3]

Discordance between the response to acute exercise and exercise training

Some exerkines are pleiotropic molecules in the sense that they can be released from different cell types under different conditions/stimuli and elicit varying physiological effects depending on the context of their release. For example, interleukin-6 (IL-6) is released from activated macrophages[4] and adipocytes within adipose tissue to elicit proinflammatory effects,[5] and consequent insulin resistance.[4,5] IL-6 is also released from contracting skeletal muscle during acute exercise, with resultant effects including potentiating insulin secretion and action, enhancing glucose uptake, and increasing fat oxidation.[6] In contrast to acute exercise where circulating IL-6 concentrations increase, García-Hermoso and colleagues' analysis[1] found that circulating IL-6 concentrations decrease at rest in response to exercise training. In fact, the exercise training-induced decreases in resting IL-6 concentrations were positively correlated with a decrease in hemoglobin A1c ($\beta = 0.44$, $p = 0.012$). Therefore, despite the increase in circulating IL-6 stimulated by acute exercise contributing to whole body glucose control during and after acute exercise, a decrease in resting IL-6 concentration in response to exercise training is also associated with improvements in glucose control.[6] Release of IL-6 from skeletal muscle is negligible at rest.[7] Therefore the decreases in circulating IL-6 elicited by exercise training is likely caused by lower IL-6 release from non-muscle sources such as adipose tissue[8] which when present and indicative of chronic, subclinical inflammation can contribute to tissue-specific insulin resistance.[9] A similar example is fetuin-A, a liver- and adipose tissue-derived glycoprotein whose elevated concentration is associated with insulin resistance.[10] Circulating concentration of fetuin-A is transiently elevated by a single bout of exercise before returning to baseline after 24 h,[11] yet is decreased in response to exercise training.[1]

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These examples illustrate that an exerkine may exhibit discordant responses to acute exercise compared to exercise training, with the discordance being characterized by aspects such as the direction of change in concentration, the cell- or tissue-specific source of the exerkine, and the metabolic consequence of exerkine action. Another important implication is that characterisation of the acute exerkine response cannot be used to infer the response to exercise training, and especially if there are several cell/tissue sources of that exerkine, and several possible mechanisms of action. This point is salient given that several recent studies report a comprehensive characterisation of the exerkine response to acute exercise,[12,13] yet the implications for metabolic health and adaptations to exercise training for many candidate exerkines remain to be described.

The residual influence of the most recent acute exercise bout

Acute exercise bouts produce short-term improvements in markers of cardiovascular and metabolic health, such as reduced blood pressure and circulating triglycerides, and increased insulin sensitivity.[9] These benefits can persist for periods of ~16−48 h,[14−17] but many benefits are not augmented or attenuated with a period of exercise training.[9,18] These observations demonstrate that acute exercise is capable of conveying discrete benefits that are independent from responses or adaptations to exercise training, an effect previously termed as "last bout effects".[18] From a methodological perspective, when investigating the effects of exercise training specifically, the presence of protracted residual influences of a recent acute exercise bout may be a confounding factor in studies where the timing of the post-training blood sample has not accounted for this phenomenon. An example would be when post-training blood samples are taken <24 h after the last exercise bout of the training intervention. In a recent multi-omic investigation, most candidate exerkines identified to change in response to acute exercise trended back towards their baseline concentration ~1 h after exercise, yet some continue to increase at 1 h after exercise.[12] Few studies have characterized the exerkine response beyond 3−8 h after exercise, but illustrative examples include 2 microRNA (out of 7 total transcripts measured) were increased,[19] and 6 metabolites were altered (5 decreased and 1 increased),[20] in circulation at 24 h after exercise.[19,20] Therefore, we have previously suggested that it may be useful to obtain blood samples at least 24 h after exercise cessation when investigating the influence of exercise training on exerkines.[3] We carefully examined the studies cited in Supplementary Table 2 by García-Hermoso et al.[1] and found that only 15 of the 41 trials analyzed reported the proximity to acute exercise from which samples were obtained.

This finding highlights a flaw in methodological and/or reporting approach that is quite pervasive in experimental studies of the response of exerkines to exercise training. Not reporting the proximity of the most recent exercise bout for blood samples taken after an exercise training intervention impacts the confidence with which results can be specifically attributed to the effect of that exercise training.

Concluding remarks

This recent systematic review by García-Hermoso et al.[1] provides an important contribution to an important aspect of the ever-expanding field of exerkine research. The findings reported provide thought-provoking insights into how exerkines are presently understood to respond to exercise training, and we intend our comments to provide useful considerations for planning and interpretation of future experiments in this field.

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Authors' contributions

IAJD contributed to the conceptualization, formal analysis, and writing of the original draft; BE contributed to the conceptualization, writing (review and editing), and supervision, as well as funding acquisition. Both authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

Both authors declare that they have no competing interests.

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