Leptin and exercise: An update

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ABSTRACT

Leptin is a multifunctional hormone (adipocytokine) involves in several biological processes. From brain metabolism, to signalling, in sexual development, inflammation, fat metabolism, as an ergogenic aid for sport and in the regulation of food intake and body weight. However, recent studies investigated some new aspects of leptin, elucidating the genetics mechanisms of production, relationships with starvation and environmental variables, and even some methodological issues in leptin measurement. Some interesting new studies deals with aerospace medicine, investigating effect of space flights on leptin. Relationships with rare disease such as HIV and with psychiatric disorders are also among the recent development of leptin studies. Physical activity remain the most important factor associate with leptin metabolism, and recent studies shows how the leptin levels are influenced by exercise in extreme sport, such ultramarathon. Relationships between leptin levels and amount of exercise is well known, but still exist some controversial point about what is the shape of the relationships (if linear or polynomial) between leptin and moderate and heavy exercise. It is emerging the need for multifactorial studies which take into account phenotype, environmental variables, nutritional status, as well as cultural aspects influencing nutrition, and controlled timing in leptin measurements.

Key words: Leptin; Exercise; Starvation; Disease.

The involvement of the multifunctional hormone Leptin in exercise metabolism and energy balance has been of interest for their potential role in ameliorating the lipid profile in different populations, to reduce adiposity and even as an ergogenic factor in sport activities. Leptin concentration in human has been shown to be connected with the regulation of eating behaviour, intermediary metabolism

and the onset of puberty as well to be a solution for subjects which obesity depends on leptin deficiency[1] but not able to treat general obesity.[2] Several reviews on leptin and exercise has been published previously.[3-8] Some of them concentrate on long and short term effects of exercise on leptin levels[5] on its relationships with energy homeostasis and appetite regulation[7] or about the effect of long training on circulating leptin levels.[9] Albeit the number of these studies, it remain several obscure points about leptin functions in exercise. For example, the effect of chronic exercise training on leptin has yielded inconsistent results.[3] Aims of this review is to make the point about the connections between exercise and leptin, considering measurement factors and their variability, connections of circulating leptin with fat mass, environmental influences on leptin levels, and other factor which relationships are still unclear with leptin, which could be possibly influenced by the omnipresence of this hormone in the human body. Some evidence from animal experiments will be also reviewed when human studies considered does not draw clear conclusions.

Literature search strategy

The overall goal of the current review was to examine the current status of the interaction of Leptin with exercise.

To this aim, an online search was performed in the database Medline, Scopus, WoS and Sport Discus. Key terms that were included and combined were: “leptin and exercise”, “leptin and sport”, “Leptin and physical activity” considering the papers published in the years 2002-2019. using different semantic arrangements of the words “Leptin” “Exercise”, “Sport and Leptin”. Inclusion criteria was to include experimental data on human or animals about leptin and exercise or be a review on leptin and exercise. 54 papers which meet the inclusion criteria were found. were found. The final search was carried out on 24 May 2019. The search strategies were combined, and duplicates were removed by Endnote software and manually. Studies in this section needed to fulfil the following inclusion criteria: 1) research conducted with human participants; 2) acute or long-term exercise intervention. Exclusion criteria were: 1) studies written in languages other than English; 2) animal or in vitro studies; 3) congress or workshop publications; 4) studies in which no exercise was performed. No limits were used concerning the year of publication. Inclusion or exclusion of articles was performed by applying the above criteria on the title and abstract in a first screening and on full texts in a second screening. Case studies and reviews were excluded, although the respective references were consulted and integrated into this revision if responding to the above-mentioned criteria. We found 54 papers, using a parallel or crossover design, meeting all the inclusion criteria.

Methodological issues in measuring leptin levels

There are differences in studies designs in influencing the results concerning the connection of leptin levels with fat mass. The time of blood sampling (immediately post exercise or delayed), the type of subjects (professional athlete, practitioners, obese, diabetics or with some other impaired metabolism), respond differently to the same training stimuli. Some studies showed leptin concentrations experience a delayed (approximately 9 h) reduction in the systemic circulation after acute resistance exercise.[10] Other studies reported a large, inter individual and intra individual variance in leptin concentration.[9] Leptin was also measured after space flights in 2 astronauts, showing a decrease in comparison to controls from 16 (preflight) to 10 (1 day postflight) and 5 ng/mL (15 days post flight) in 1 subjects, with a return to baseline levels after 15 days, but any change in the second subject.[11] The two astronauts showed very different level of leptin, one subject showing almost twice the values than the other, according to findings about the variability of leptin levels in recreational sportsmen.[9] This result, together with the observed muscle mass loss confirm some previous findings which shown a relationships between leptin levels and hand grip strength.[12]

Genetics and leptin

From a genetic point of view, recent studies with knockdown mice adipose tissue explants show convincing evidence for adipogenin, a regulator of adipocyte differentiation, as the novel causal gene in the SLC32A1 locus influencing leptin levels.[13] The effect of aerobic exercise, seems to be mediated by the presence of selected polymorphism of LEP (leptin) and LEPR (leptin receptors) genes.[14]

Starvation

Starvation (heavy diet, 35-50% of fat mass reduction) reduces circulating leptin[15] as does energy deficit of about 5500 cal/day for 3 days.[16] In opposition to this finding, during the Arabic Ramadan, despite a significant loss of fat mass in healthy adults, no reduction in circulating leptin was observed.[17]

Training

Recently, leptin levels (free leptin index), have also been confirmed to be predicted both by fat mass and body weight reduction.[18] Further, ultraendurance training produced reduction of leptin levels similar to starvation.[19] Lean high-level athletes, striving to maintain a low body weight for the requirements of sport, shows lower levels of leptin in comparison to athletes with higher fat mass.[20] An interesting review[6] emphasized the effect of low leptin levels induced by heavy training and insufficient energy intake in female athletes in causing hypothalamic amenorrhea, a potential health-

treating condition. This evidence was previously confirmed in rock climbers, a category of athletes that should control the body weight strictly.[21] One year training for rowing for a season did not modify resting basal leptin levels but it attenuated the post exercise-induced reduction in leptin.[22] Not only leptin was found to lower immediately after an intense exercise in rowers, but also the rate of decrease was found to be associated with the distance rowed.[23] The same association can be found in half marathoners, ski alpinism (45 km) and ultramarathon (100 km).[24] Also, the postexercise decrease in leptin levels was confirmed by other studies, showing a rapid decrease after a 20 minutes running on a treadmill at the 70% VO2max, with a rapid return to basal values after an hour of supine rest.[25] Interestingly, in horses, leptin level was influenced by 6 months of heavy training only in young horses, who showed a marked decrease (10,8 *vs.* 1,1 ng/mL), while older horses and saddle stallion didn't.[26] Interestingly, albeit the environment has a strong influence on energy expenditure, we found only one paper considering this factor in interaction with leptin. Environmental temperature (ranging from 7 to 33 degree C), who can be supposed influence energy balance, has no effect in leptin concentration after exercise.[27] A recent metanalysis study,[3] concluded that he decrease of leptin with exercise is independent from fat mass, even if the reduction was more pronounced with further weight losses, for exercise protocols lasting more than 2 weeks. The signalling mechanisms involved in this process are starting to be elucidated and were identified in the hypothalamic extracellular signal-regulated kinase-1/2 (ERK1/2) as a key mediator of the thermoregulatory effect of leptin.[28] Increased brighter sunlight exposure has been shown to be correlated with lower fasting insulin (which is associated with leptin) (-1.27% [95% confidence interval: -2.09, -0.47] per extra hour of bright sunlight, and lower triglyceride (-1.28% [-2.07, -0.50]) levels, but this large study failed to find an association with outdoor temperature.[29]

Different sports, different leptin?

Some difference seems to exist between different sports in reducing plasma leptin. Small side games seems to be more effective than cycling in reducing leptin levels.[30] On the contrary, others findings indicate any effect of exercise on leptin[31] and any association with fat mass changes or perceived hunger.[32] It was observed[33] that moderate-to-vigorous physical activity was associated with a more favourable profile of inflammatory markers, independent of relevant cardiometabolic disease risk factors including central obesity, thus also indicating leptin to be independent from fat mass. An interesting study in subjects living with HIV, so with depressed immune system, show the reduction of fat mass ad different body sites without any significant reduction in leptin levels after 16 weeks of training.[34]

It is quite clear that leptin is associated with fat mobilization, as demonstrated in marathoners, who shows higher leptin values than controls, and in overtrained athletes, who showed lower leptin levels compared to control population due to iperconsumption of leptin.[35] In adolescents[36] circulating leptin is associate with vigorous physical activity, independently of body fat. Leptin was found to be inversely correlated with exercise and positively correlated with estradiol in post menopausal women also independently from body fat.[37] Leptin has showed to acutely decrease in the blood even after a single bout of anaerobic exercise.[38] On the contrary, others studies found leptin to decrease, independently from weight loss, only after aerobic, but not anaerobic, exercise in heavy trained sledogs and greyhounds.[39] This result was confirmed also after a prolonged military camp training.[40] In this case, together with leptin, there was a significant decrease in fat mass. Kinetic of leptin during an ultramarathon races lasting 6 days, showed a decrease in respect to baseline in the first days of the race, followed by a marked increment in the last days (2.44±0.13 2.53±0.19 1.86±0.10e 2.35±0.13 2.74±0.14 2.75±0.15).[41] It was shown a lowering of leptin[9] during exercise and a return to baseline with recovery, with a time-lapse of 24 hours for decrease and plateauing during the racing, and 72 hours to re-establish the basal levels. Also it was reported[9] an inter-individual variability of leptin expressed as CV% of 53.6%, and an average intra-individual variability was only 34.1% (range 28.7%-41.1%) during the study period. The same trend in leptin, was observed during a simulated 9 days bike racing and subsequent recovery.[9] Still in mountain ultramarathoners, but on a single race of 64 km, leptin at rest is lower than in controls, and decreased post exercise to value > 1ng/mL,[42] however this was known from the earliest studies on leptin and exercise.[43] The relationship of circulating leptin with exercise was demonstrated also in children, exercising moderately at least 30 min per day, 5 days per week[44] and also there is a relationship of Leptin with maximal oxygen consumption[45] in children, independently from fat mass. Recent evidences in adults, which shows that both vigorous exercise (resistance training) than continuous steady state exercise has an effect in leptin reduction,[46] confirmed these findings. This latter result was later extended to the association of light-PA time, moderate-vigorous-PA time, sedentary time and body composition with Leptin levels in a large cohort of adolescents.[47] It was demonstrated[48] a chronic low level of leptin in over trained athletes, thus candidate leptin reduction as a marker of overtraining.

Leptin effect on the CNS

The presence of leptin receptors in the CNS, has been postulated to be a signalling regulating factor for satiety and famine. In the brain was discovered the long form of leptin receptors (LEPR) in areas known to be important for the regulation of energy expenditure, and of short forms of LEPR in peripheral organs as regulators of peripheral energy balance, and also of LEPR in neurons (associated

for example with the neuropeptide Y, which act in decreasing energy expenditure.[49] In addition, psychological stress can stimulate production of biochemical hormones and peptides such as leptin, ghrelin, and neuropeptide Y.[50] In the CNS, neurons located in the Arcuate and Ventromedial Hypothalamic Nuclei and the medullary area postrema, have been identified as the main sites for leptin receptors.[51] Considering the effect of leptin on the CNS, it is worth noting that has been observed that leptin concentration mediates the association of cardiorespiratory fitness and muscular strength with academic performance in adolescents.[52] On the opposite, an increase of leptin levels has been observed in the early stages of psychosis.[53]

Conclusions

After more than 25 years from the discovery,[54] Leptin continues to stimulate researches about its association with exercise. This interest is partially due to the lack of clarity about some fundamental issues. Some studies has evidenced some methodological issues such as the timing of measurements, which can influence the values measured. Other lacks of definitive conclusions about a definitive relationships of leptin with exercise. These can be abscribed to the difficulties in controlling all the factors which influence energy homeostasis together with exercise: food, every day mobility out of the exercise and the difficulty in precisely quantify it, internal and individual modification determined by a same training protocols adopted and difficulties to standardize energy expenditure and environmental factors such as temperature and humidity (seldom controlled in the interventional studies about leptin and exercise), specific phenotype studied and difference within the same categories of subjects (*e.g.* high level athletes *vs.* lower level of qualification athletes), physiological interaction with special states (nutrient deficiency, puberty, diabetes or prediabetes, athletics amenorrhea). However some interactions are well demonstrated, for example the dependence of circulating level of leptin from fat storage and mobilization in the body, and the decrease of blood plasma leptin with exercise. Other issues remains obscure, for example its relationships with the immune system, ergogenic effect of leptin, interaction with fatigue and recovery (poor sleep). However, analysing the available literature, exercise appear to be the strongest regulator of circulating leptin levels. This concept is supported by a number of evidences in different subjects (children, athletes, sedentary, obese). Of course, the expanding body of knowledge about the interactions of leptin and exercise, including environmental factors, nutrition and genetics, open several news perspectives for research.

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