

Conjugated Linoleic Acid and Exercise may Share One Biochemical Pathway to Induce Fat-loss

Ácido Linoleico Conjugado e Exercício podem Partilhar Uma Via Bioquímica para Induzir a Perda de Gordura

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ABSTRACT

Conjugated linoleic acid is a functional ingredient which induces fat-loss in various high quality studies in humans. Although the effect is usually moderate in size, both *in vitro* studies with conjugated linoleic acid and studies on mice suggest that this effect is real and has a functional basis. Evidence, from *in vitro* studies and from studies in mice, shows that conjugated linoleic acid affects the expression of a number of genes or gene products which are involved in fat accumulation in adipose tissue. Based on scientific literature we hypothesize that these genes are part of an AMP-kinase dependent body composition regulating (ABC) network that functions both in adipocytes and muscle cells. This network may affect not only adipose tissue but also, lean body mass and exercise endurance and is probably also activated by doing exercise. The consequence of this model is that exposure to conjugated linoleic acid and exercise together may help to enhance fat-loss since they share a common biochemical pathway.

KEYWORDS: Conjugated linoleic acid, Sports nutrition, Exercise, Fat-loss, Biochemical pathway

RESUMO

O ácido linoleico conjugado é um ingrediente funcional, que induz a perda de gordura, indicado em vários estudos em humanos de elevada qualidade. Embora o efeito seja geralmente moderado em dimensão, tanto os estudos *in vitro* com o ácido linoleico conjugado como os estudos em ratinhos sugerem que este efeito é real e tem uma base funcional. Evidências, de estudos *in vitro* e de estudos com ratinhos, demonstram que o ácido linoleico conjugado afecta a expressão de um número de genes ou produtos de genes que estão envolvidos na acumulação de gordura no tecido adiposo. Com base na literatura científica sugerimos a hipótese de que esses genes são parte de uma rede de regulação da composição corporal dependente da AMP-quinase, que funciona tanto em adipócitos como em células musculares. Esta rede pode afectar não só o tecido adiposo, mas também, a massa magra e resistência ao exercício e, provavelmente, é também activada pela realização de exercício. A consequência desse modelo é que a exposição ao ácido linoleico conjugado e exercício em conjunto podem ajudar a melhorar a perda de gordura, desde que partilhem uma via bioquímica comum.

PALAVRAS-CHAVE: Ácido linoleico conjugado, Nutrição desportiva, Exercício, Perda de gordura, Via bioquímica

INTRODUCTION

Conjugated linoleic acid (CLA) is known to consistently induce fat loss in humans, but to a limited extent (1,2). However, both *in vitro* studies with CLA and studies with CLA in mice suggest that this effect is real and has a functional basis. Recently Kennedy et al published a review on the mechanism by which CLA induces fat-loss (3). This work describes that CLA may reduce obesity by at least 5 different mechanisms. However it appears puzzling how a simple fatty acid can have so many different body fat reducing mechanisms of action at the same time. Therefore we looked for a unifying hypothesis. This article describes such a hypothesis and discusses the consequences of this hypothesis if it was correct.

The Adiposity Related Genes Affected by CLA Treatment

CLA affects the expression and or functional activity of a number of genes or gene products (proteins) which are involved the regulation of fat accumulation in adipose tissue. These genes include AMPK (4-7), CPT1 (3, 8-13), Sirt1 (5), PPAR-gamma (13,14), PGC1 (7), and UCP 1/2/3 (11, 15-17). Of all these genes, AMPK appears to have a central role in the mechanism of fat-loss by CLA as

the gene expression observed in cells treated with Metformin, a pharmacological tool to activate AMPK (18), is very similar to the gene expression as induced by exposure of cells to CLA (5) and since AMPK is activated rapidly after exposure to CLA (6).

Effects of Adiposity Genes on Endurance Capacity and Lean Body Mass

While studying the effects of AMPK, CPT1, SIRT1, PPAR-gamma, PGC1 and UCP1/2/3 on adiposity the attention was drawn to the fact that these genes do not only share effects on adiposity but also on lean body mass and endurance capacity (Table 1). For CLA it has already been shown that it increases lean body mass in humans (19) and improves endurance capacity in mice (20). However it was not described before that possibly the same genes are involved in improving exercise endurance.

The AMPK-Dependent Body Composition Regulating Network

Since most of the genes mentioned above (AMPK, CPT-1, SIRT-1, PPAR-gamma, PGC-1 and UCP-1/2/3) are involved in regulating metabolism, in fat loss from adipose tissue, in increases in lean

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TABLE 1: Genes affecting adiposity also affect lean body mass and endurance capacity

	AMPK ↑	CPT1 ↑	SIRT1 ↑	PPAR-gamma ↓	PGC1 ↑	UCP 1/2/3 ↑
Fat-mass ↓	21 [*] , 22 ^{**}	24 [*] , 25	28 [*] , 29 ^{**}	31 [*] , 32 ^{**}	33 [*]	34 [*] , 35 ^{**}
Lean body mass ↑	23 ^{**}	26	?	31 [*] , 32 ^{**}	33 [*]	36 [*]
Endurance capacity ↑	22 ^{**}	27 ^{**}	28 [*] , 29 ^{**} , 30 ^{**}	20 ^{***}	33 [*]	?

A change in the activities of genes affecting adiposity (expressed horizontally), not only reduce *in vivo* fat-mass, but can also increase lean body mass and increase endurance capacity. ? : No data known; *: References from genetic intervention; **: References for pharmacological intervention; ***: Data for CLA

body mass and in improving endurance capacity it seems reasonable to suspect that they are all part of one biological network.

Therefore scientific literature was evaluated with respect to functional inter-relationships between these genes and gene products. This evaluation resulted in the "AMPK-dependent body-composition-regulating network" (ABC-network) of genes as presented in Figure 1. This network is essentially the same as the energy sensing network as described by Canto (37). For the purpose of this evaluation the potential regulatory role of PPAR gamma was added to Canto's network. This network appears to work both in adipocytes as in muscle cells as both are relatively rich in PPAR gamma receptors. Exercise probably also activates this network as exercise activates AMPK (by producing AMP from ATP), increases beta-oxidation and down-regulates PPAR gamma. (38).

We suspect that CLA mainly affects the AMPK-dependent body composition regulating network by acting as a functional PPAR gamma antagonist (14) since other functional PPAR gamma antagonists like tanshinone IIA (32), ginsenoside Rg3 (39), capsaicin (40), berberine (41) and ginsenoside Rh2 (42) have similar effects on metabolism. Since PPAR gamma is a nuclear receptor involved in gene expression of various genes, inhibition of PPAR gamma signaling by CLA will result in an altered gene expression of various genes. Uncoupling protein-2 (UCP2) is known to be up-regulated by a genetic reduction of PPAR gamma-signaling in muscle (43). Functionally this reduced PPAR gamma signalling is similar to the effect of a functional PPAR gamma receptor antagonist like CLA (14). Uncoupling of the mitochondrial oxidative phosphorylation either by increased expression or activation of uncoupling proteins (44) or by chemical uncoupling by 2,4, dinitrophenol (45) results in increased AMP formation and increased NAD⁺/NADH ratio. These effects are known either directly or indirectly to activate AMPK, CPT1 and SIRT1 (46). This model therefore explains how just one basic mechanism of action of CLA (functional PPAR gamma antagonism) can affect not only body composition but also improve endurance capacity by activating the ABC network.

Interaction of CLA with Exercise, Nutraceuticals and Drugs

As explained above, all genes depicted in the ABC-network of Figure 1 result in reduced adiposity if their activities are changed in the direction as mentioned in Figure 1. Also exercise (52), treatment with metformin (23), AICAR (22), carnitine (25), resveratrol (30), SIRT1720 (55), tanshinone

IIA (32), ginsenoside Rh2 (42), CLA (1), Dinitrophenol (DNP) (35) and beta-Lapachone (56), all depicted in Figure 1, can result in reduced adipogenicity. Of these treatments at least resveratrol (30), metformin (57), AICAR (22) and CLA (20) have shown to improve endurance. This suggests that all these treatments may enhance the effect of CLA by working on the same network. A potent and early effect of CLA is activation of AMPK. Other activators of AMPK including metformin (57), AICAR (22) and exercise (58, 59) have similar effects on metabolism and endurance capacity. For this reason Narkar positioned AICAR as an "exercise mimetic" (22). The following effects on biology, which are typically caused by exercise, are known to be induced by exposure to CLA: Reduced fat-mass (1), increased lean body mass (19), improved exercise endurance (20, 60), increased strength (60, 61) increased bone mineralisation (62), reduced inflammatory disease (63) and protection against cancer (64). In mice CLA and exercise affect the same biochemical network and share many similar effects on physiology, and therefore CLA may also qualify as an "exercise mimetic", at least in mice.

Effect of CLA on ABC-Network Activation in Humans

The data as described above are mainly gathered from studies in mice and *in vitro* systems because studies in humans usually are not very suitable to investigate biochemical networks or mechanisms. However there is evidence to suggest that the ABC-network is also affected by CLA in humans: Effects on adiposity (1) and lean body mass (19) have been confirmed in humans. Mechanistic evi-

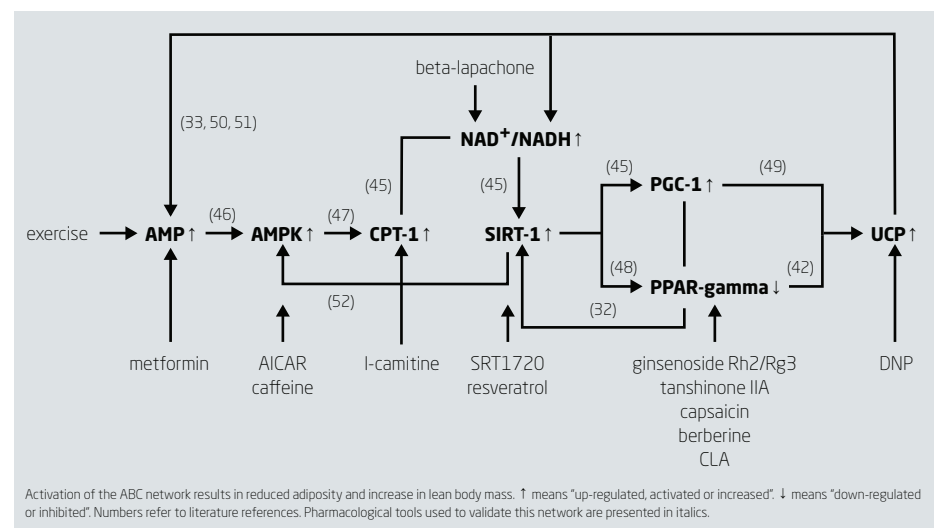
dence for activity of the ABC network activated by CLA in humans was provided by Herrmann et al (17): Exposure of humans to a chronic dose of CLA which is sufficient to induce fat-loss resulted in an increase in UCP2 expression as well as a decrease in PPAR gamma expression in adipose tissue. Since these markers in combination with fat loss and increase in lean body mass can be seen as biomarkers for activity of the ABC-network it is tempting to speculate that CLA also activates the ABC-network in humans.

To date two studies were done to measure the effects of CLA on strength. Both these studies (60, 61) showed statistically significant increase in strength. An initial small trial to test the effect of CLA on performance was performed by Colakoglu in 2006 (65). In this trial CLA showed consistent improvement of endurance but the effects were not statistically significant. Statistically significant effects of CLA on endurance have been published by Ha et al in 2010 (60). However more work is needed to quantify this effect.

Although no final proof exists that CLA activates the ABC network in humans, the totality of evidence does suggest that CLA activates the ABC network in humans since evidence suggest that CLA reduces fat-mass (1), increases lean body mass (19) and strength (60, 61) up-regulates UCP2 (17) and down-regulates PPAR gamma (17).

CRITICAL ANALYSIS

A weight-loss claim for CLA has not been approved by EFSA. Also fat-loss as described for CLA in this article is not observed in all human trials (66-69). Therefore when all studies on CLA are included, the effects of CLA on weight-loss or fat-loss are not conclusive. It is therefore important to mention that fat-loss as described in this article is only observed in a selection of studies: These studies were selected as being high quality (conducted according EFSA guidelines) and they were further limited to those using volunteers with a BMI between 25 and 32 (the target population for CLA). Also, only studies were selected which use a dose of ≥ 3 grams of mixed isomers of CLA for a period of ≥ 12 weeks, to assure adequate dosing.

FIGURE 1: The AMPK-dependent Body Composition (ABC) regulating network

CLA and exercise appear to share various effects on biochemistry and physiology. However taking CLA is not exactly the same as doing exercise. Exercise activates the ABC pathway by consuming ATP and producing AMP. CLA does so by acting as a functional PPAR receptor antagonist. Exercise is known to increase insulin sensitivity. Since mechanistically CLA has the opposite effect on insulin sensitivity as Rosiglitazone (70) (a PPAR gamma receptor agonist), this may explain why this health benefit is not observed for CLA. Exercise also induces temporally metabolic acidosis, increased body temperature, hypoxia and hormonal changes which may promote health in a way that is not necessarily mimicked by CLA. Since fat-loss effects of CLA are generally stronger if CLA is taken in combination with exercise and CLA is likely to potentiate the ABC network-related effects of exercise, it is advisable to use CLA in combination with exercise to promote fat-loss, but not instead of exercise.

CONCLUSIONS

The totality of data evaluated in this article, suggest that CLA activates the ABC-network not only in animals but possibly also in humans. This explains several of the physiological effects as observed for CLA. This network is probably also activated by doing exercise.

DISCLAIMER

The author is employed by Stepan Specialty Products B.V., which commercially produces CLA.

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