Casual Friday Presents

mTor/AMPK Balance

A BIOGENETIX CLINICAL PRESENTATION

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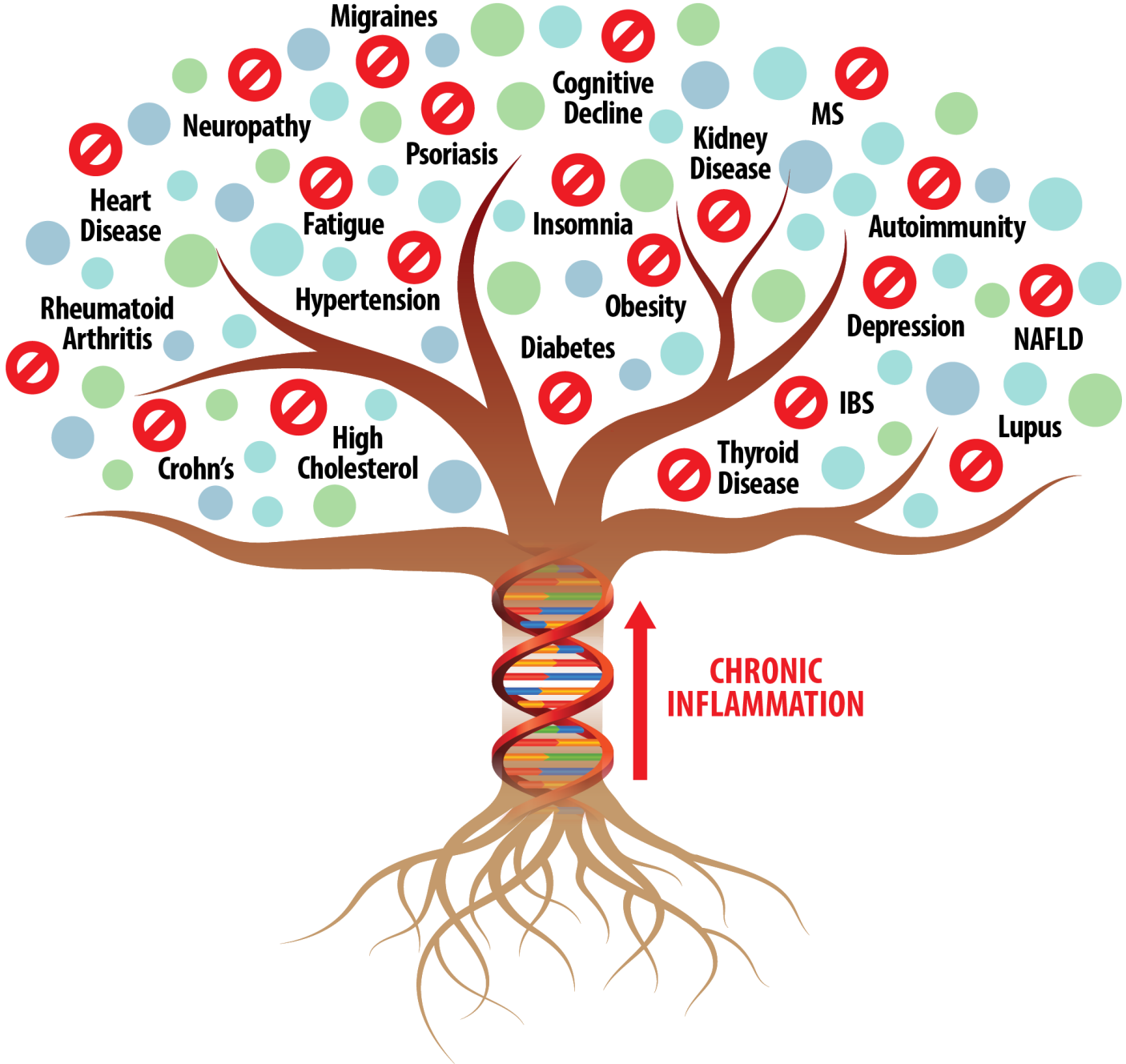
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Autoimmunity
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION

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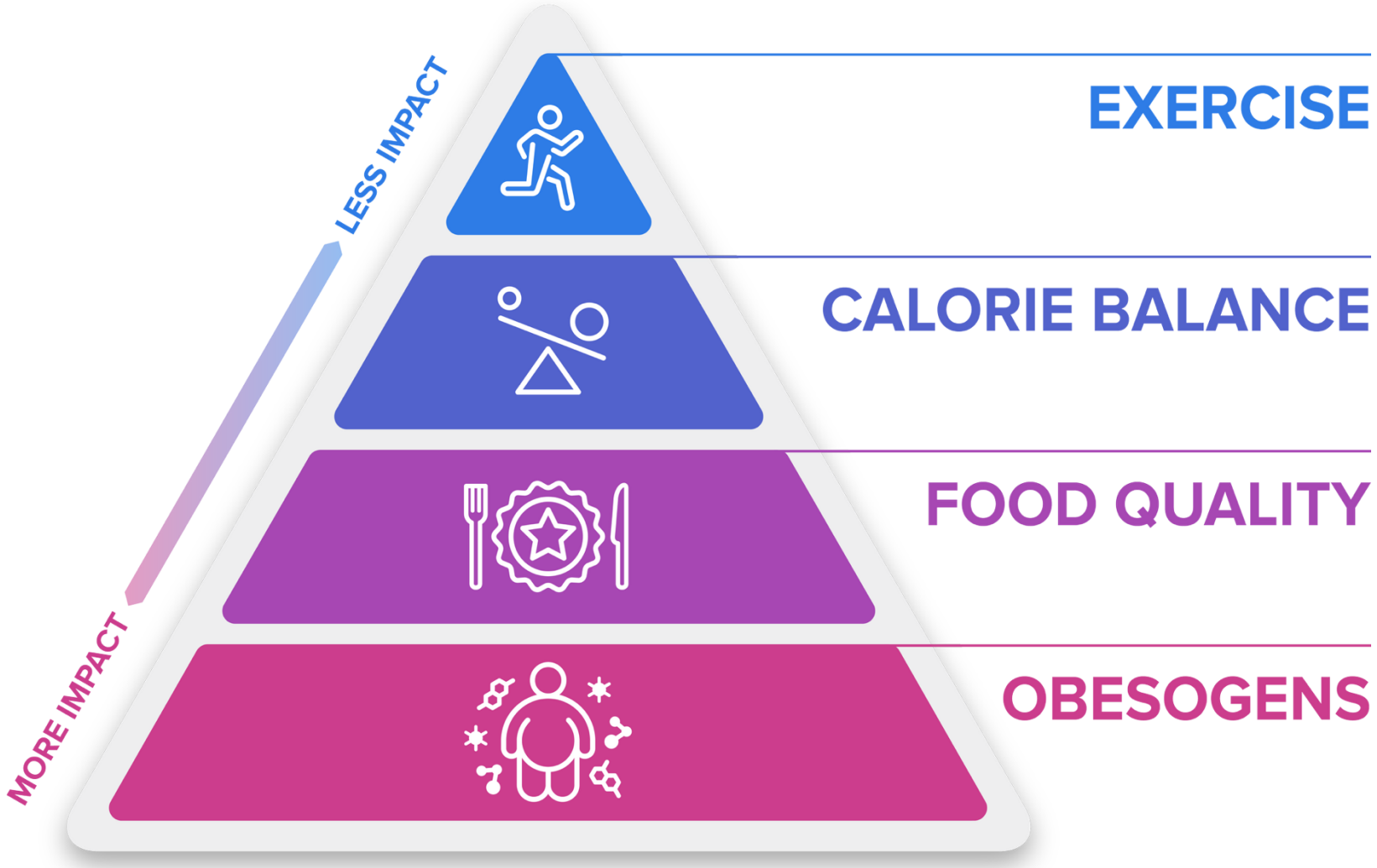
LESS IMPACT
MORE IMPACT
EXERCISE
CALORIE BALANCE
FOOD QUALITY
OBESOGENS

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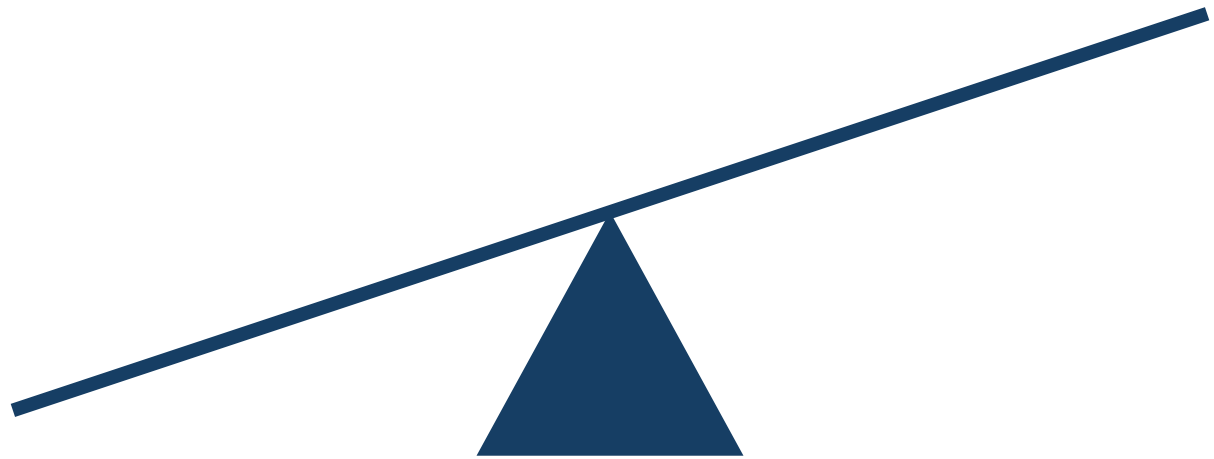

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Review > Crit Rev Food Sci Nutr. 2012;52(5):373-81. doi: 10.1080/10408398.2010.500245.

Cross-talk between AMPK and mTOR in regulating energy balance

Jia Xu [1], Jian Ji, Xiang-Hua Yan

Affiliations + expand

PMID: 22369257 DOI: 10.1080/10408398.2010.500245

Energy balance is maintained by a complex homeostatic system involving some signaling pathways and "nutrient sensors" in multiple tissues and organs. Any defect associated with the pathways can lead to metabolic disorders including obesity, type 2 diabetes, and the metabolic syndrome. The 5'-adenosine monophosphate-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR) appear to play a significant role in the intermediary metabolism of these diseases. AMPK is involved in the fundamental regulation of energy balance at the whole body level by responding to hormonal and nutrient signals in the central nervous system and peripheral tissues that modulate food intake and energy expenditure. Mammalian target of rapamycin (mTOR),is one of the downstream targets of AMPK functions as an intracellular nutrient sensor to control protein synthesis, cell growth, and metabolism. Recent research demonstrated the possible interplay between mTOR and AMPK signaling pathways. In this review,

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AMPK

•AMPK — The metabolic stress sensor (like a low battery mode)

•5'-Adenosine Monophosphate-Activated Protein Kinase

Triggered when: Cellular energy is low → high AMP/ATP ratio, low glucose, exercise, fasting, calorie restriction, many polyphenols (e.g., resveratrol, quercetin in smaller doses).

•The main job (catabolism: breaking down / conserving):

- ↑ Glucose uptake
- ↑ Fatty acid oxidation
- ↑ Mitochondrial genesis
- ↑ Autophagy
- ↓ Protein synthesis, lipid synthesis, cell growth & proliferation

***Inhibits mTOR**

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mTOR

•mTOR — The Nutrient & Growth Sensor (A lot of resources mode)

•mechanistic Target Of Rapamycin (two complexes, but mTORC1 is main)

Triggered when: Nutrients are abundant → amino acids (especially leucine), insulin/growth factors (IGF-1, insulin), high energy, normal O2.

•The main jobs (anabolic: building):

- ↑ Protein synthesis
- ↑ Lipid synthesis
- ↑ Cell growth, proliferation, hypertrophy
- ↓ Autophagy (strongly suppresses autophagy)

*Turned on via amino acid exposure, calorie intake.

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The AMPK mTOR See-Saw (Most Important Crosstalk)

Condition	AMPK Activity	mTOR Activity	Action	Triggers
Fed + insulin spike	Low	High	Build muscle/proteins, store energy	Big meal, carbs + protein
Fasting / calorie restriction	High	Low	Recycle, fat burning, autophagy ↑	16+ hr fast, low calories
Endurance Training	High	Low–medium	Mitochondrial adaptation, fat oxidation	Long run/cycling
Resistance Training	Variable/low	Very high	Muscle protein synthesis ↑	Lifting + post-workout meal
Chronic overfeeding/obesity	Low	Chronically high	Insulin resistance, reduced autophagy	Constant high nutrient intake

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Autophagy

•Autophagy – the main process where cells recycle damaged organelles, misfolded proteins, etc.

mTOR strongly blocks autophagy

AMPK strongly promotes autophagy:

•Most longevity, anti-aging, and anti-cancer strategies that work in animal studies (calorie restriction, fasting, metformin, rapamycin, exercise, spermidine, etc.) leverage ↑ AMPK + ↓ mTORC1 → ↑ autophagy + better mitochondrial health.

*Prolon style interventions using food but avoiding specific amino acids (leucine, methionine, cysteine) to dampen mTOR activation.

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The AMPK–mTOR Balance in Weight Loss Scenarios

Scenario	AMPK Level	mTOR Level	Net Impact	Mechanism
Calorie deficit / fasting	High	Low	Strong fat loss, improved insulin sensitivity	Fat oxidation ↑, lipogenesis ↓, autophagy ↑
Endurance exercise	High	Suppressed	Fat burning, mitochondrial adaptation	Energy stress → AMPK dominance
Resistance training + fed state	Variable/low	High	Muscle building > fat loss (short-term)	mTOR drives anabolism
Chronic overeating	Low	High	Weight/fat gain, insulin resistance	Anabolic overload, reduced oxidation
GLP-1 drugs (e.g., semaglutide)	Enhanced	Reduced	Significant weight loss (15–20%+ in trials)	Liver/adipose mTOR↓ + AMPK↑, appetite ↓

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PHARMACOLOGY & THERAPEUTICS | AUGUST 01 2006

Berberine, a Natural Plant Product, Activates AMP-Activated Protein Kinase With Beneficial Metabolic Effects in Diabetic and Insulin-Resistant States

Yun S. Lee; Woo S. Kim; Kang H. Kim; Myung J. Yoon; Hye J. Cho; Yun Shen; Ji-Ming Ye; Chul H. Lee; Won K. Oh; Chul T. Kim; Cordula Hohnen-Behrens; Alison Gosby; Edward W. Kraegen; David E. James; Jae B. Kim

Berberine has been shown to have antidiabetic properties, although its mode of action is not known. Here, we have investigated the metabolic effects of berberine in two animal models of insulin resistance and in insulin-responsive cell lines. Berberine reduced body weight and caused a significant improvement in glucose tolerance without altering food intake in *db*/*db* mice. Similarly, berberine reduced body weight and plasma triglycerides and improved insulin action in high-fat–fed Wistar rats. Berberine downregulated the expression of genes involved in lipogenesis and upregulated those involved in energy expenditure in adipose tissue and muscle. Berberine treatment resulted in increased AMP-activated protein kinase (AMPK) activity in 3T3-L1 adipocytes and L6 myotubes, increased GLUT4 translocation in L6 cells in a phosphatidylinositol 3′ kinase–independent manner, and reduced lipid accumulation in 3T3-L1 adipocytes. These findings suggest that berberine displays beneficial effects in the treatment of diabetes and obesity at least in part via stimulation of AMPK activity.

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P: INSULIN ACTION—ADIPOCYTE BIOLOGY | JUNE 01 2022

American Diabetes Association. | Publications

1297-P: Berberine Derivatives as Novel Antidiabetes Agents Targeting Intestinal AMPK and Antimicrobial Peptide-Controlled Gut Microbiome FREE

ERYUN ZHANG

Mammalian 5′-AMP-activated protein kinase (AMPK) is a key nutrient sensor for maintaining cellular energy status and a known therapeutic target for glucose control in type 2 diabetes (T2D) . Despite current understandings of its well-established roles in regulating glucose metabolism in various tissues, AMPK functions in the intestine, the first-line organ for nutrient processing, remains largely elusive. We have uncovered a novel link between intestinal AMPK activation and brown adipose tissue (BAT) thermogenic regulation through modulating the anti-microbial peptide (AMP) -controlled gut microbiota and their metabolites. Therefore, the intestinal *AMPK-AMP-microbiota-BAT axis* is a potential target for the treatment of T2D. Berberine, a quaternary ammonium protoberberine alkaloid with an isoquinoline scaffold isolated from medicinal herbs, has been used to treat T2D in animal models as well as human trials, while offsetting renal, cardiovascular, hepatic, and respiratory risks. However, its poor bioavailability severely limits its application and development. As such, there is a dire need to explore structural modifications of berberine to obtain better pharmacological properties and elucidate its underlying mechanisms of action. Berberine can activate AMPK indirectly by inhibition of mitochondrial respiration in the adipocyte, myotubes and liver; however, its effects on intestinal AMPK are still unknown. We have successfully synthesized natural and non-natural novel berberine derivatives. We will determine their antidiabetes effects and elucidate the underlying mechanisms of action in targeting the intestinal AMPK-AMP pathways for T2D treatment. Moreover, our study will provide a better structure-activity relationship to guide the future design of berberine derivatives with higher potency and improved bioavailability.

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> Biochem Biophys Res Commun. 2005 Jul 8;332(3):885-91. doi: 10.1016/j.bbrc.2005.05.035.

Alpha-lipoic acid increases insulin sensitivity by activating AMPK in skeletal muscle

Woo Je Lee [1], Kee-Ho Song, Eun Hee Koh, Jong Chul Won, Hyoun Sik Kim, Hye-Sun Park, Min-Seon Kim, Seung-Whan Kim, Ki-Up Lee, Joong-Yeol Park

Affiliations + expand

PMID: 15913551 DOI: 10.1016/j.bbrc.2005.05.035

Triglyceride accumulation in skeletal muscle contributes to insulin resistance in obesity. We recently showed that alpha-lipoic acid (ALA) reduces body weight and prevents the development of diabetes in diabetes-prone obese rats by reducing triglyceride accumulation in non-adipose tissues. AMP-activated protein kinase (AMPK) is a major regulator of cellular energy metabolism. We examined whether ALA lowers triglyceride accumulation in skeletal muscle by activating AMPK. Alpha2-AMPK activity was decreased in obese rats compared to control rats. Administration of ALA to obese rats increased insulin-stimulated glucose disposal in whole body and in skeletal muscle. ALA also increased fatty acid oxidation and activated AMPK in skeletal muscle. Adenovirus-mediated administration of dominant negative AMPK into skeletal muscle prevented the ALA-induced increases in fatty acid oxidation and insulin-stimulated glucose uptake. These results suggest that ALA-induced improvement of insulin sensitivity is mediated by activation of AMPK and reduced triglyceride accumulation in skeletal muscle.

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> Hepatology. 2008 Nov;48(5):1477-86. doi: 10.1002/hep.22496.

Alpha-lipoic acid decreases hepatic lipogenesis through adenosine monophosphate-activated protein kinase (AMPK)-dependent and AMPK-independent pathways

Keun-Gyu Park [1], Ae-Kyung Min, Eun Hee Koh, Hyoun Sik Kim, Mi-Ok Kim, Hye-Sun Park, Yong-Deuk Kim, Tae-Seung Yoon, Byoung Kuk Jang, Jae Seok Hwang, Jae Bum Kim,

Fatty liver is common in obese subjects with insulin resistance. Hepatic expression of sterol regulatory element binding protein-1c (SREBP-1c), which plays a major role in hepatic steatosis, is regulated by multiple factors, including insulin, adenosine monophosphate-activated protein kinase (AMPK), liver X receptors (LXRs), and specificity protein 1. Alpha-lipoic acid (ALA), a naturally occurring antioxidant, has been shown to decrease lipid accumulation in skeletal muscle by activating AMPK. Here we show that ALA decreases hepatic steatosis and SREBP-1c expression in rats on a high fat diet or given an LXR agonist. ALA increased AMPK phosphorylation in the liver and in cultured liver cells, and dominant-negative AMPK partially prevented ALA-induced suppression of insulin-stimulated SREBP-1c expression. ALA also inhibited DNA-binding activity and transcriptional activity of both specificity protein 1 and LXR.

Conclusion: These results show that ALA prevents fatty liver disease through multiple mechanisms, and suggest that ALA can be used to prevent the development and progression of nonalcoholic fatty liver disease in patients with insulin resistance.

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SUPPLEMENT FACTS

Serving size: 2 Capsules Servings per container: 60	Amount Per Serving	% Daily Value
Biotin	190 mcg	633%
Berberine HCl	500 mg	**
Alpha-Lipoic Acid	250 mg	**

** Daily Value Not Established

Other Ingredients: Capsule (hypromellose and water), dicalcium phosphate, magnesium stearate, silica, and microcrystalline cellulose.

Does Not Contain: Wheat, gluten, corn, yeast, soy, animal or dairy products, fish, shellfish, peanuts, tree nuts, egg, ingredients derived from genetically modified organisms (GMOs), artificial colors, artificial sweeteners, or artificial preservatives.

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Glucose Support Bundle

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