Casual Friday Series

Advancements in Weight Loss Applications, Pt III

A Biogenetix Clinical Presentation

BIOGENETIX.COM

Disclaimer

- *Information in this presentation is not intended to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

US Doctors' Group Adopts New Policy on Healthy Weight Assessment

By Nancy Lapid
June 15, 2023

Add to Email Alerts

REUTERS

1145

(Reuters) - The American Medical Association (AMA) on Wednesday said it will advise doctors to pay less attention to body mass index (BMI) in determining if a patient is at a healthy weight, saying the measure does not predict disease risk equally well across racial and ethnic groups.

BMI, a ratio of weight to height, has long been used to define underweight, "normal" weight, overweight, obesity and morbid obesity, despite mounting evidence that it is an inaccurate predictor of health risks on an individual level.

At the influential physician group's annual meeting in Chicago, members voted adopt a new policy that says BMI should be just one factor in determining whether a patient is at a healthy weight. Other measures such as body composition, belly fat, waist circumference, and genetic factors are also important, the AMA said.

There have been "issues with using BMI as a measurement due to its historical harm (and) its use for racist exclusion," the AMA said.

'Staggering' Weight Loss and Benefits in Body Composition With Tirzepatide

Becky McCall
May 19, 2023

52

321

DUBLIN — Substantial reductions in body weight across body mass index (BMI) categories, as well as improved body composition, were achieved with tirzepatide (Mounjaro) in adults for chronic weight management, according to the latest results of the SURMOUNT-1 study.

The new analysis showed that up to 63% of participants achieved a reduction in body weight of at least 20%, and all three tirzepatide doses (5 mg, 10 mg, and 15 mg) led to substantial, clinically meaningful, and sustained body-weight reduction compared with placebo at 72 weeks of follow-up.

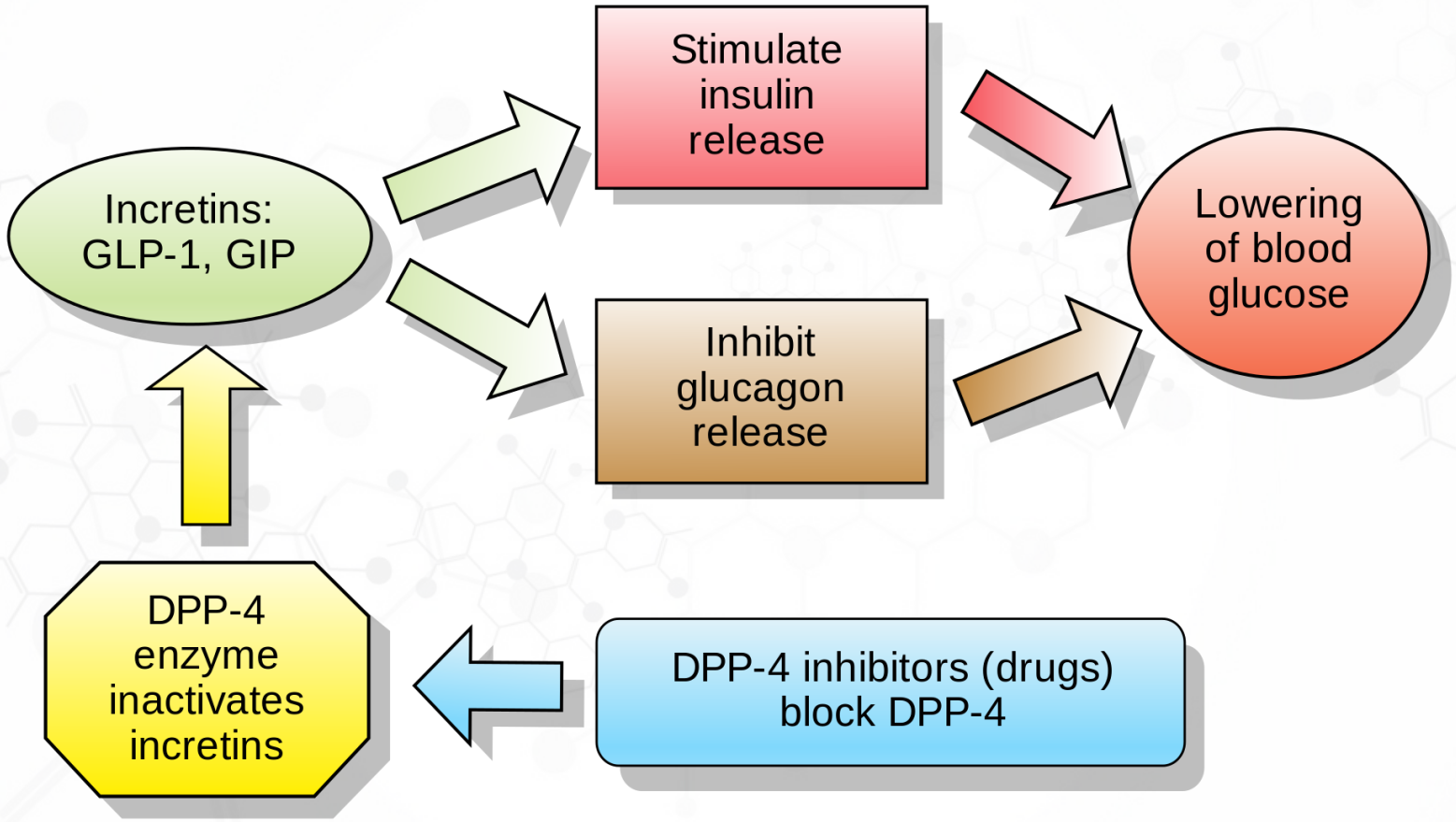
Mean weight loss was –16.0%, –21.4%, and –22.5% with tirzepatide 5 mg, 10 mg, and 15 mg compared with –2.4% for placebo (all $P < .001$ vs placebo). And among participants taking the highest 15-mg dose of tirzepatide, 96%, 90%, and 78% of patients achieved weight reductions of at least 5%, 10%, and 15%.

Mounjaro (tirzepatide) is currently the only class of drug that is both a glucagon-like peptide-1 (GLP-1) and a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist. GLP-1 and GIP are incretins, naturally occurring hormones in your body that stimulate insulin secretion in response to increased blood glucose levels after you eat.

GLP-1 works to slow digestion, causing you to feel fuller longer after eating. Tirzepatide imitates these hormones helping to promote weight loss in patients with obesity.

In comparison, Ozempic is solely a GLP-1 agonist and only activates one hormone receptor.

https://joinfound.com/blogs/posts/mounjaro-vs-ozempic#:~:text=Lilly%27s%20tirzepatide%20imitates%20these%20hormones,only%20activates%20one%20hormone%20receptor.



By Clinical Cases, Ilmari Karonen - Drawn in Inkscape by Ilmari Karonen based on w:Image:Incretins and DPP 4 inhibitors.jpg from http://casesblog.blogspot.com/2006/11/dpp-4-inhibitors-for-treatment-of.html (uploaded by author), CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=1540751

Diabetologia. 2017; 60(8): 1390–1399.
Published online 2017 May 19. doi: 10.1007/s00125-017-4289-0
PMCID: PMC5491562
PMID: 28526920

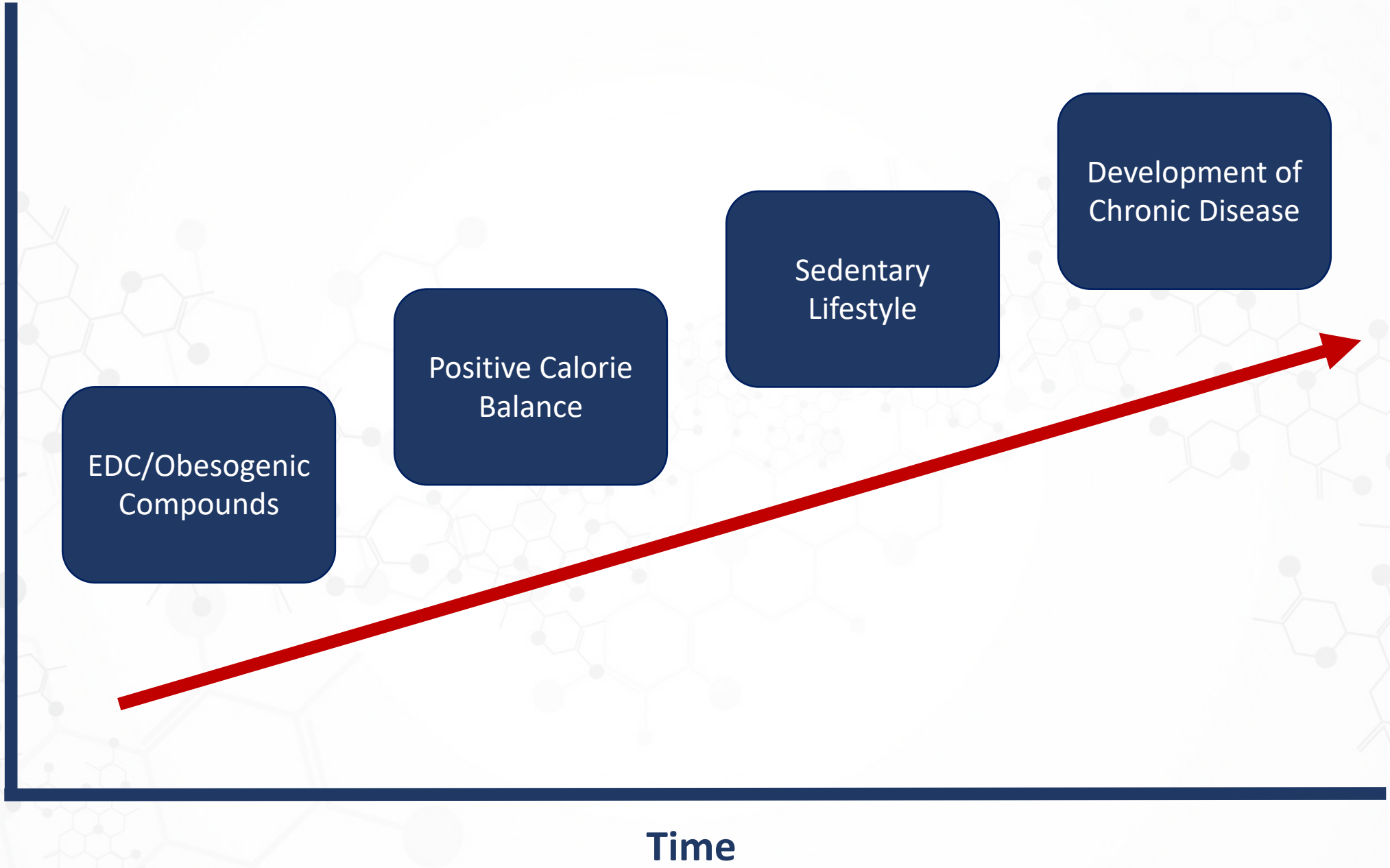
Effects of semaglutide on beta cell function and glycaemic control in participants with type 2 diabetes: a randomised, double-blind, placebo-controlled trial

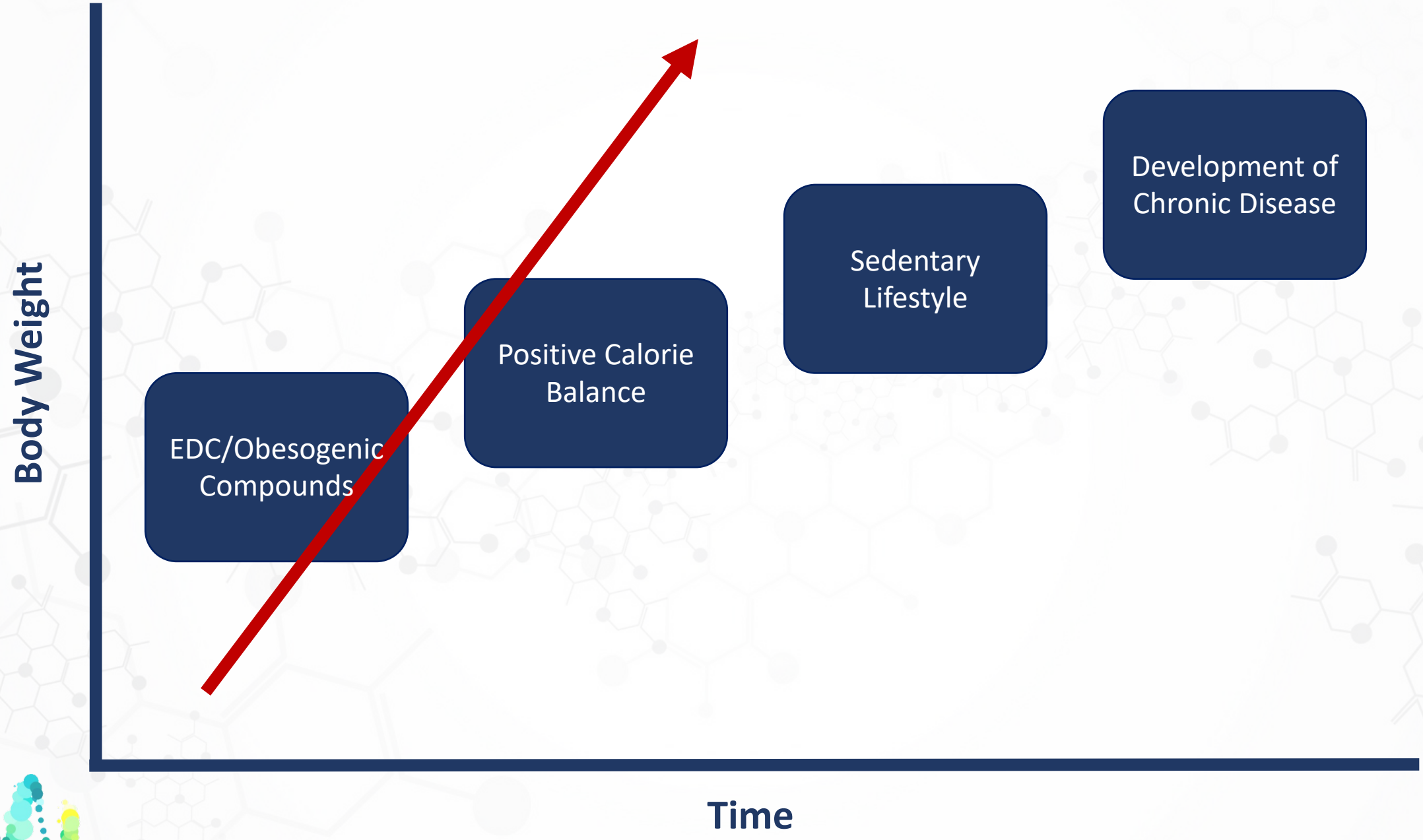
Christoph Kapitza,[✉1] Kirsten Dahl,[2] Jacob B. Jacobsen,[2] Mads B. Axelsen,[2] and Anne Flint[2]

Author information · Article notes · Copyright and License information Disclaimer

This study investigated the effects of 12 weeks of once-weekly s.c. semaglutide treatment on various aspects of beta cell function in participants with type 2 diabetes. It was demonstrated by IVGTT that semaglutide treatment increased first- and second-phase insulin secretion threefold and twofold, respectively, compared with placebo. Correspondingly, levels of glucagon and glucose were decreased with semaglutide vs placebo. Similar findings have been reported for once-daily liraglutide, which significantly increased both first- and second-phase insulin secretion after 14 weeks of treatment in participants with type 2 diabetes [7].

Results from the AST under hyperglycaemic conditions showed that maximal insulin capacity had improved following semaglutide treatment. Despite insulin levels prior to the test being higher in semaglutide-treated participants than in participants receiving placebo, insulin levels increased immediately in response to the stimulus and remained high for the duration of the test. This effect could contribute to the reported efficacy of semaglutide in improving glycaemic control [23], particularly as recent research suggests that individuals with sustained endogenous insulin-secreting capacity may benefit more from GLP-1RA therapy [24].


Body Weight
EDC/Obesogenic Compounds
Positive Calorie Balance
Sedentary Lifestyle
Development of Chronic Disease
Time


Body Weight
EDC/Obesogenic Compounds
Positive Calorie Balance
Sedentary Lifestyle
Development of Chronic Disease
Time

Front Endocrinol (Lausanne). 2021; 12: 780888.
Published online 2021 Nov 25. doi: 10.3389/fendo.2021.780888
PMCID: PMC8655100
PMID: 34899613

Obesogens: How They Are Identified and Molecular Mechanisms Underlying Their Action

Nicole Mohajer, [1] Chrislyn Y. Du, [2] Christian Checkcinco, [2] and Bruce Blumberg[1,2,3,*]

Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Obesity has become a present-day pandemic affecting people of all ages across the world. According to the World Health Organization, the prevalence of global obesity has nearly tripled since 1975 with a continued upward trajectory (1). In 2016, the WHO reported more than 1.9 billion adults as overweight, with 650 million of those adults as obese. The prevalence of obesity in children has continued to rise in the U.S alone, despite the nation's efforts to promote better nutrition practices and increase physical activity levels in the educational system (2). In 2019, a staggering 38.2 million children under the age of 5 were reported as overweight or obese, worldwide (1). Comorbidities associated with obesity affect nearly all physiological systems and lead to serious health complications including mortality and a lowered quality of life. Obesity contributes to a growing list of health complications including insulin resistance, cardiovascular diseases, airway dysfunctions, metabolic syndrome, kidney disease, osteoarthritis, skin diseases, reproductive disorders, and cancer (3, 4) and death from COVID-19 (5). In addition to physiological comorbidities, the burden of obesity affects the individual's psychological well-being, leading to higher stress and depression. Obesity often presents together with depression and negative self-image in both children and adults, creating a vicious cycle where the conditions potentiate each other (3, 6). Those who suffer from depression are 58% more likely to develop obesity, and those who are obese are 55% more likely to develop chronic depression (7). Obesity makes it less likely for students to stay in school past the 12th grade, independently of their parent's socioeconomic status (8). Similarly, lower education levels have been linked to higher weight gain and obesity (9). Obesity places a financial and emotional burden on individuals, their families, and the nation at large when loss of productivity and loss of work is considered. The CDC reported the national obesity-related cost to be $147 billion in 2008, however, more recent data from 2014 estimates the cost of obesity and its comorbidities to be closer to $2 trillion dollars (10, 11). It is estimated that the annual cost of obesity in the U.S will rise $48-66 billion each year throughout 2030 (4). Therefore, the severe consequences of obesity on both individual and population-level health demand that urgent attention be paid to this worsening pandemic.

In Vitro Studies

Bisphenol A (BPA)	Used in personal products, household care products, and plastics	PPARγ activator	Induces the differentiation of adipocytes	(36, 37)
Parabens	Used as cosmetic preservatives and as bactericides/fungicides	PPARγ activator	Induces the differentiation of adipocytes	(36)
Phthalates	Used in cosmetics, pharmaceuticals, paints, medical equipment, and plastics	PPARγ activator	Induces the differentiation of adipocytes	(36)

Front Endocrinol (Lausanne). 2021; 12: 780888.
Published online 2021 Nov 25. doi: 10.3389/fendo.2021.780888
PMCID: PMC8655100
PMID: 34899613

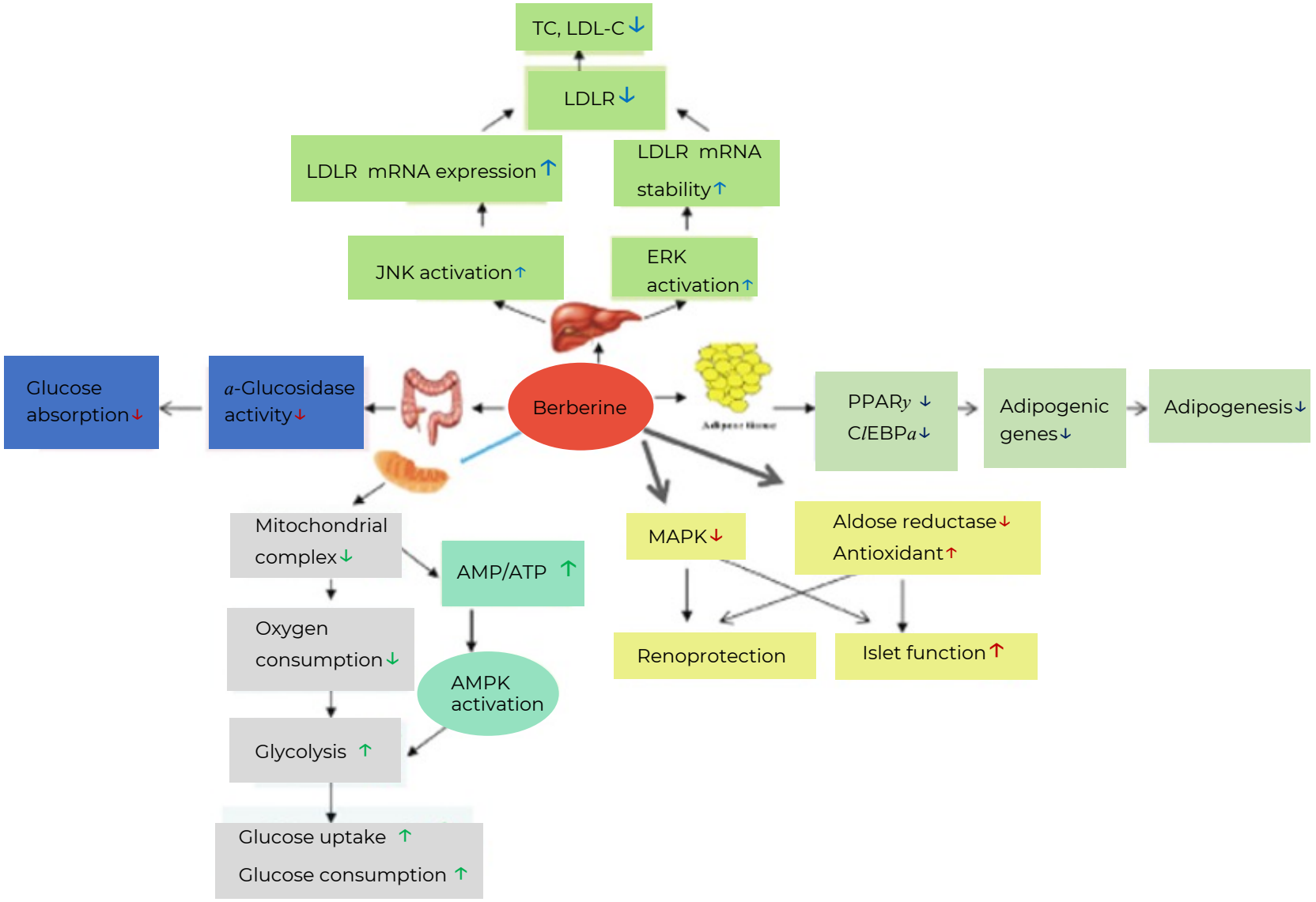
Obesogens: How They Are Identified and Molecular Mechanisms Underlying Their Action

Table 3

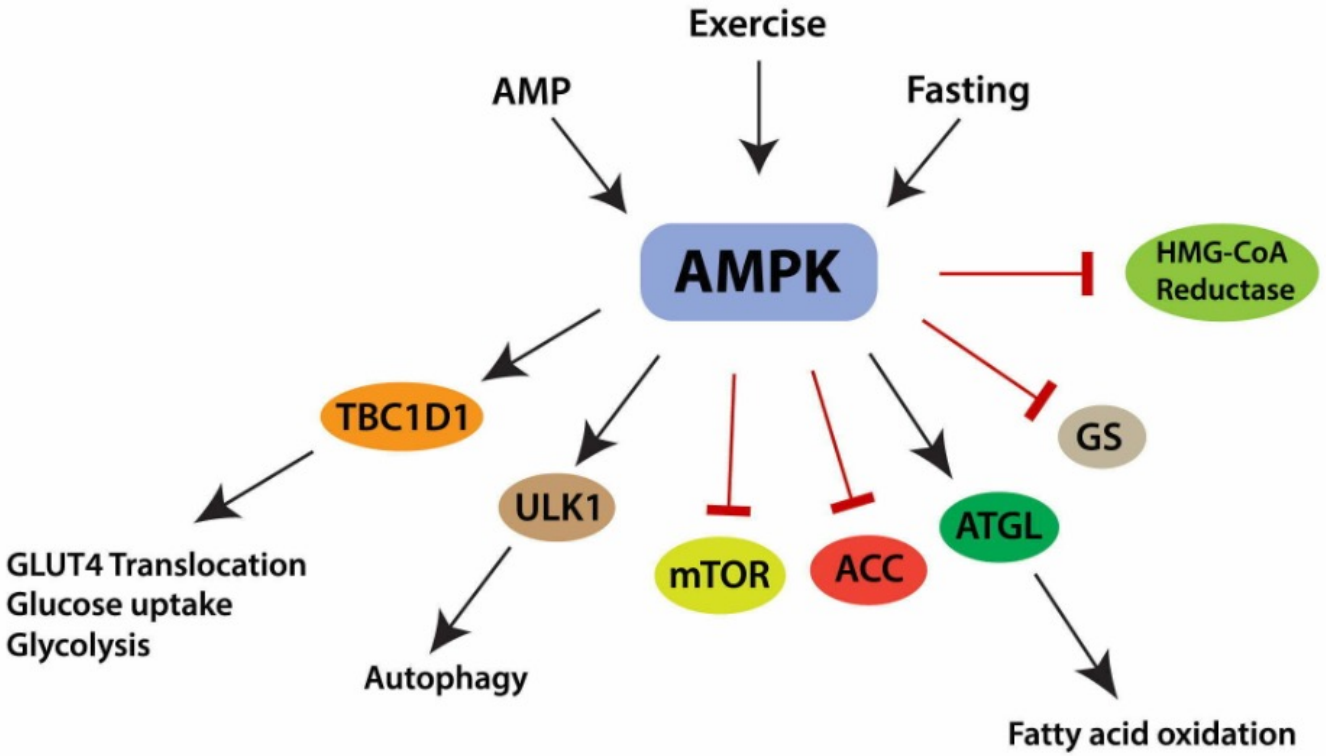
Chemical obesogens and their effects on thermogenic fat and adipose tissue.

Chemical	Source/Use	Proposed Mechanism	Effects	References
Bisphenols (A, F, S)	Chemical used to make polycarbonate plastics and epoxy resins. Found in the lining of food packaging.	Acts as an estrogen receptor agonist androgen, receptor antagonist	Shifts mesenchymal stem cell commitment and differentiation towards adipogenesis	(111, 112)
Dichlorodiphenyltrichloroethane (DDT) & dichlorodiphenyldichloroethylene (DDE)	Found in pesticides. DDE is a metabolite of DDT.	Acts as an estrogen receptor agonist, androgen receptor antagonist.	Induces a loss of BAT thermogenesis and affects the SNS that innervates BAT and WAT.	(77, 111, 113)
Arsenic	Polluted ground water	Lowers the expression of PPARγ, UCP1 and PGC1. Activates Estrogen Receptor	Inhibits the differentiation of BAT.	(115, 116)

- ↑ Glucose uptake through induction of glycolysis/AMPK activation
- ↓ Adipogenesis through inhibition of PPARγ and C/EBPα function
- ↓ Glucose absorption by inhibition of α-glucosidase
- ↑ Pancreatic islet cell function via aldose reductase and MAPK inhibition and antioxidant activity
- ↓ LDL through activation of ERK and JNK pathways



Yin J et al. *Acta Pharmaceutica Sinica B*. 2012;2(4):327-334. doi:10.1016/j.apsb.2012.06.003
Zhang Q et al. *Evid Based Complement Alternat Med*. 2011;2011:924851. doi:10.1155/2011/924851
Zhou L et al. *Metabolism*. 2007;56(3):405-412. doi:10.1016/j.metabol.2006.10.025



Catabolic processes promoted by AMPK

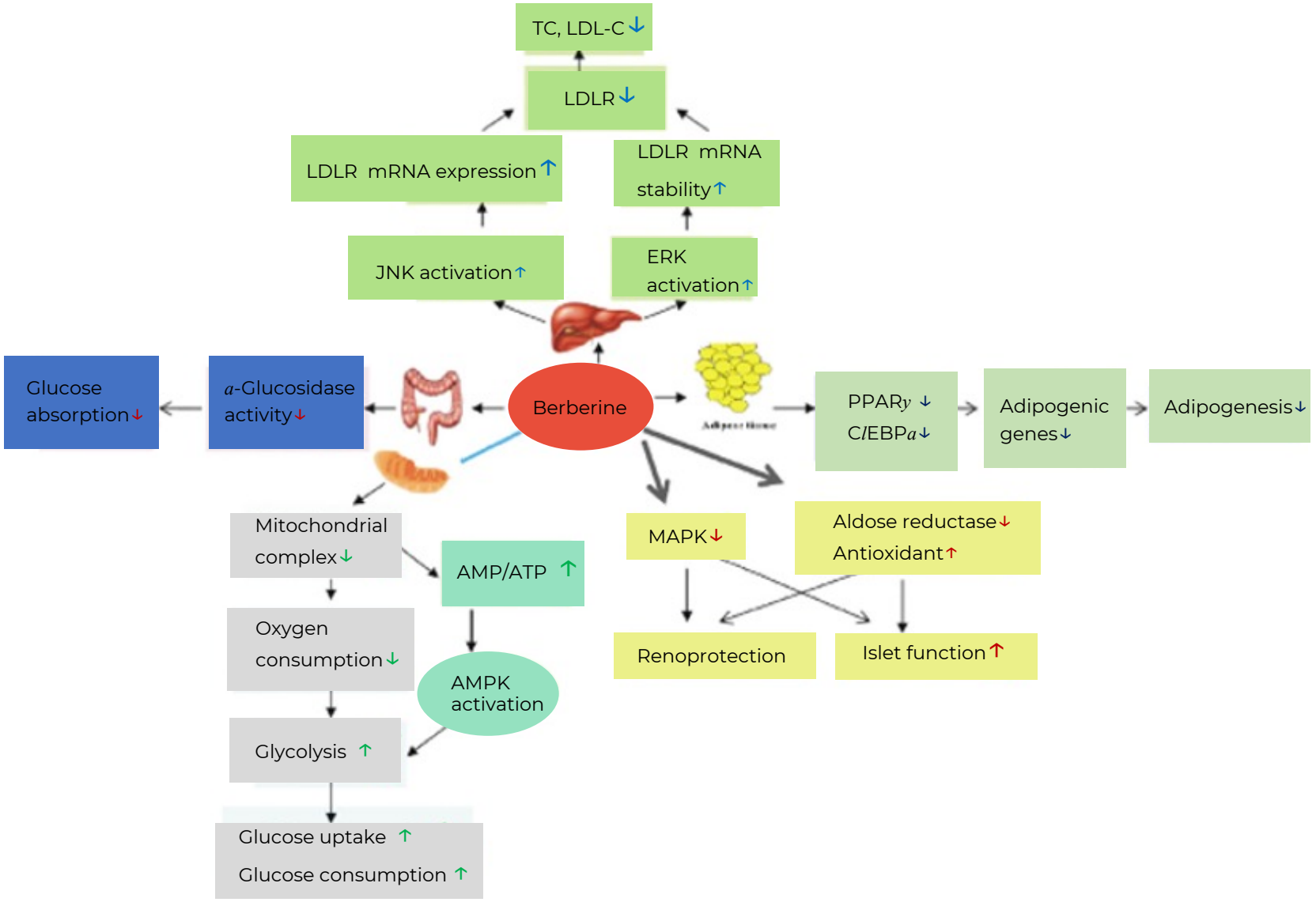
- Fatty acid oxidation
- Glucose uptake
- Glycolysis
- Autophagy
- Mitochondrial biogenesis

Anabolic processes inhibited by AMPK

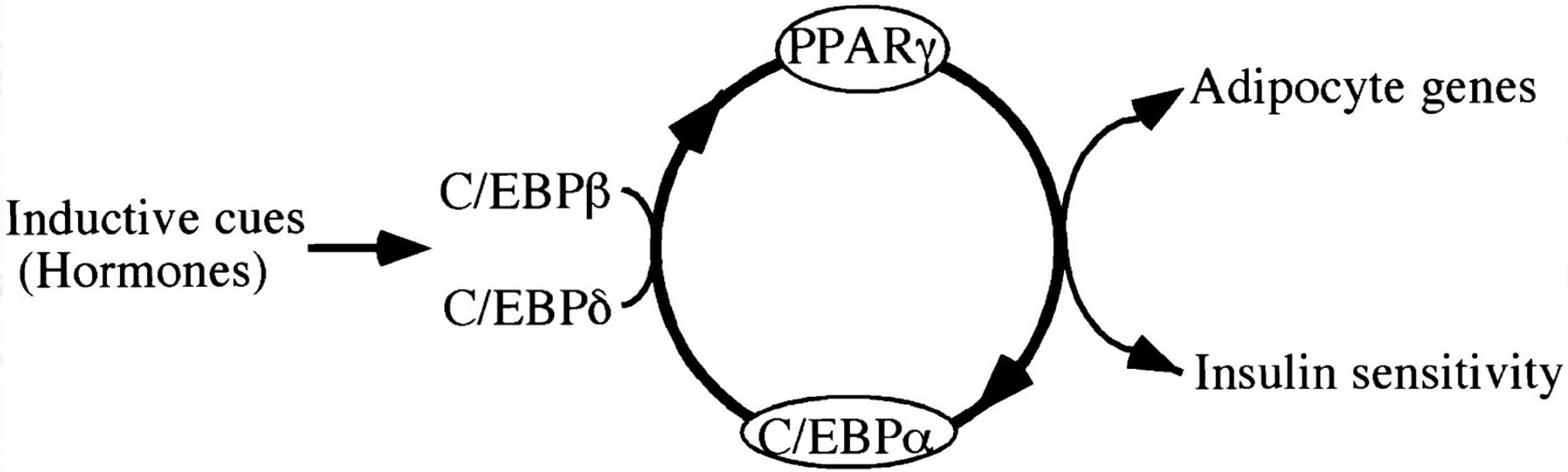
- Fatty acid synthesis
- Glycogen synthesis
- Gluconeogenesis
- Cholesterol synthesis

https://www.legerepharm.com/wp-content/uploads/2020/10/AMPKpathway-copy-01.jpg

- ↑ Glucose uptake through induction of glycolysis/AMPK activation
- ↓ Adipogenesis through inhibition of PPARγ and C/EBPα function
- ↓ Glucose absorption by inhibition of α-glucosidase
- ↑ Pancreatic islet cell function via aldose reductase and MAPK inhibition and antioxidant activity
- ↓ LDL through activation of ERK and JNK pathways

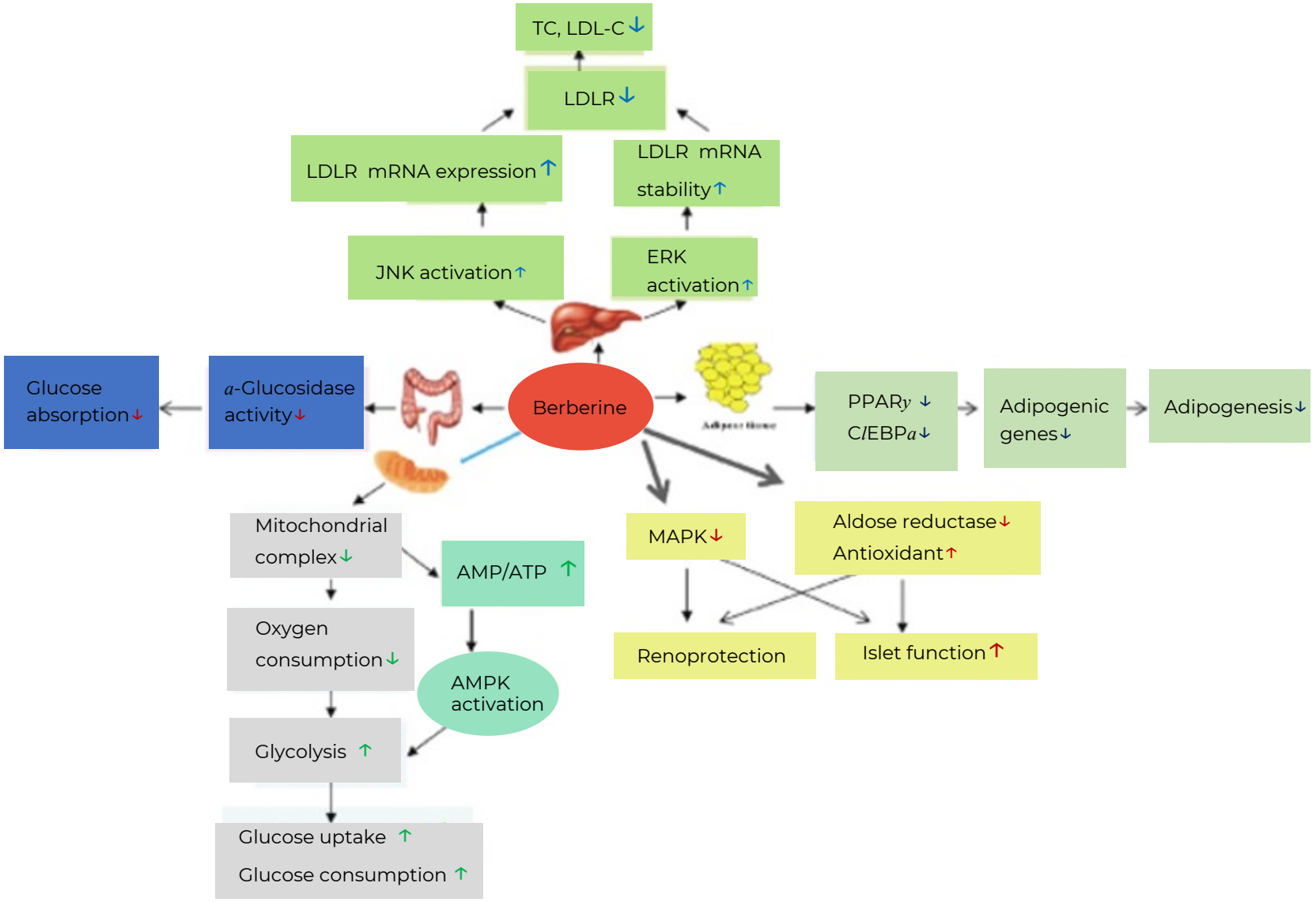


Yin J et al. *Acta Pharmaceutica Sinica B*. 2012;2(4):327-334. doi:10.1016/j.apsb.2012.06.003
Zhang Q et al. *Evid Based Complement Alternat Med*. 2011;2011:924851. doi:10.1155/2011/924851
Zhou L et al. *Metabolism*. 2007;56(3):405-412. doi:10.1016/j.metabol.2006.10.025



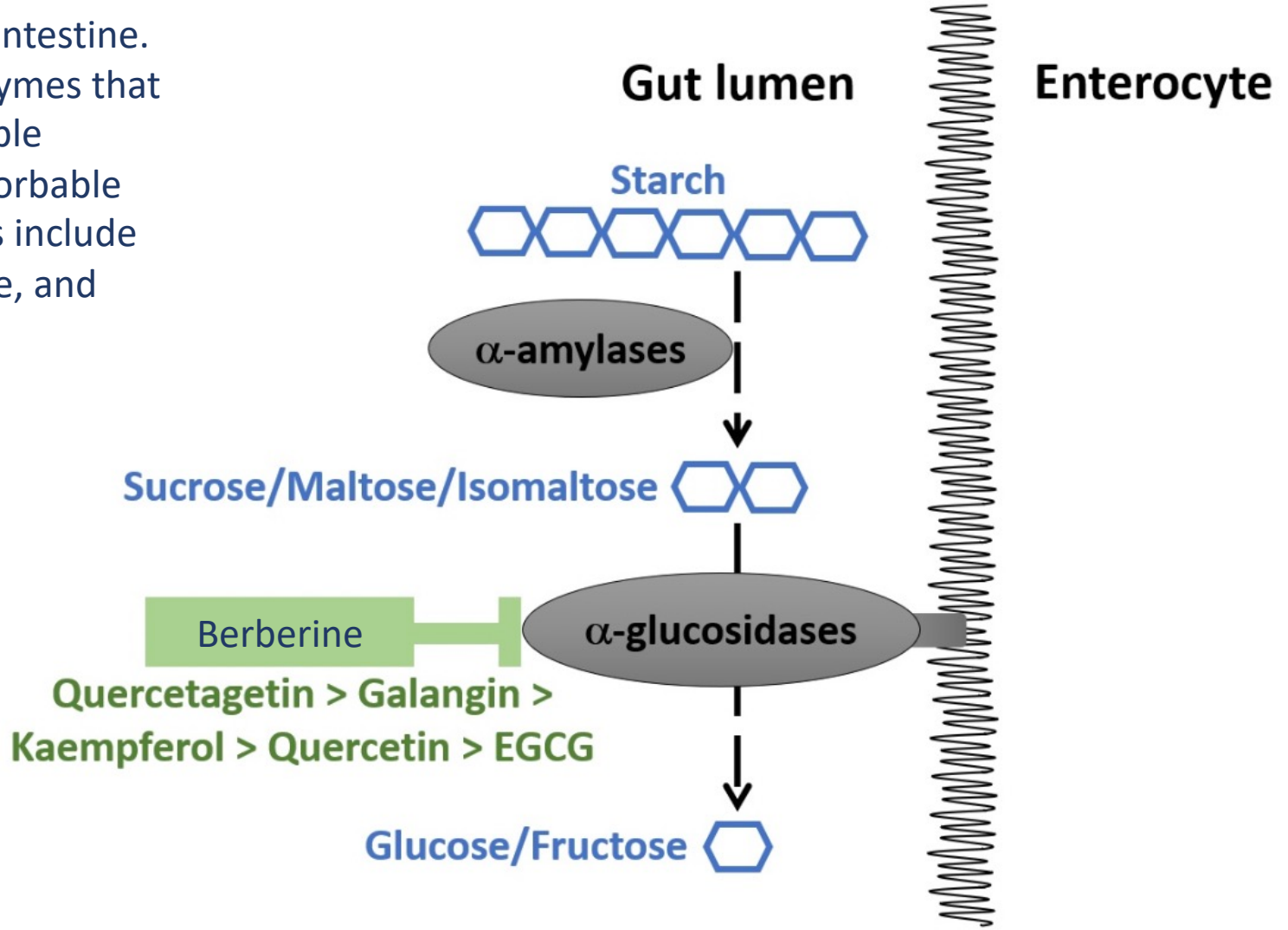
https://ars.els-cdn.com/content/image/1-s2.0-S1097276500803068-gr6_lrg.jpg

- ↑ Glucose uptake through induction of glycolysis/AMPK activation
- ↓ Adipogenesis through inhibition of PPARγ and C/EBPα function
- ↓ Glucose absorption by inhibition of α-glucosidase
- ↑ Pancreatic islet cell function via aldose reductase and MAPK inhibition and antioxidant activity
- ↓ LDL through activation of ERK and JNK pathways



Yin J et al. *Acta Pharmaceutica Sinica B*. 2012;2(4):327-334. doi:10.1016/j.apsb.2012.06.003
Zhang Q et al. *Evid Based Complement Alternat Med*. 2011;2011:924851. doi:10.1155/2011/924851
Zhou L et al. *Metabolism*. 2007;56(3):405-412. doi:10.1016/j.metabol.2006.10.025

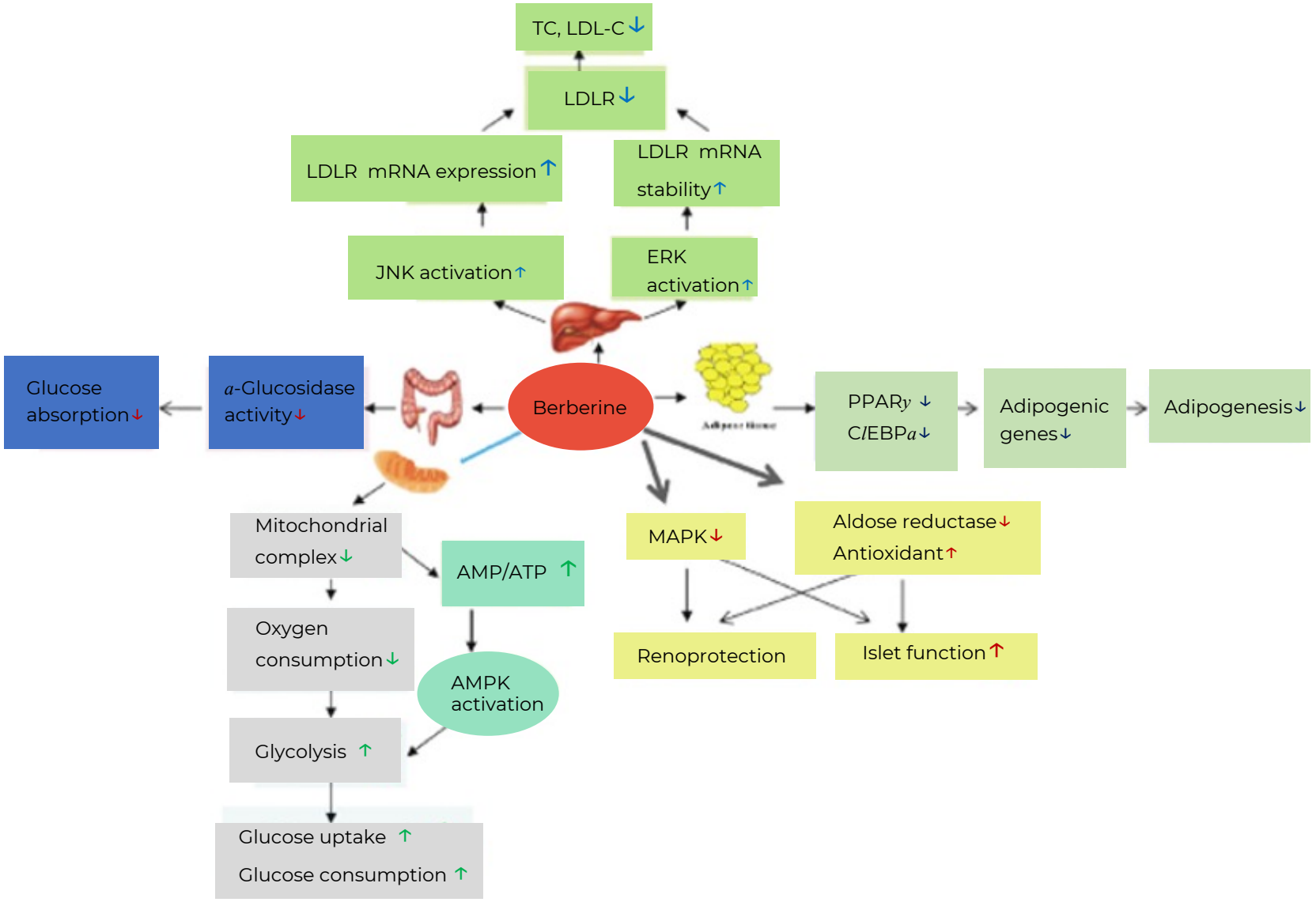
Alpha-glucosidase inhibitors [such as berberine] inhibit the absorption of carbohydrates from the small intestine. They competitively inhibit enzymes that convert complex non-absorbable carbohydrates into simple absorbable carbohydrates. These enzymes include glucoamylase, sucrase, maltase, and isomaltase.



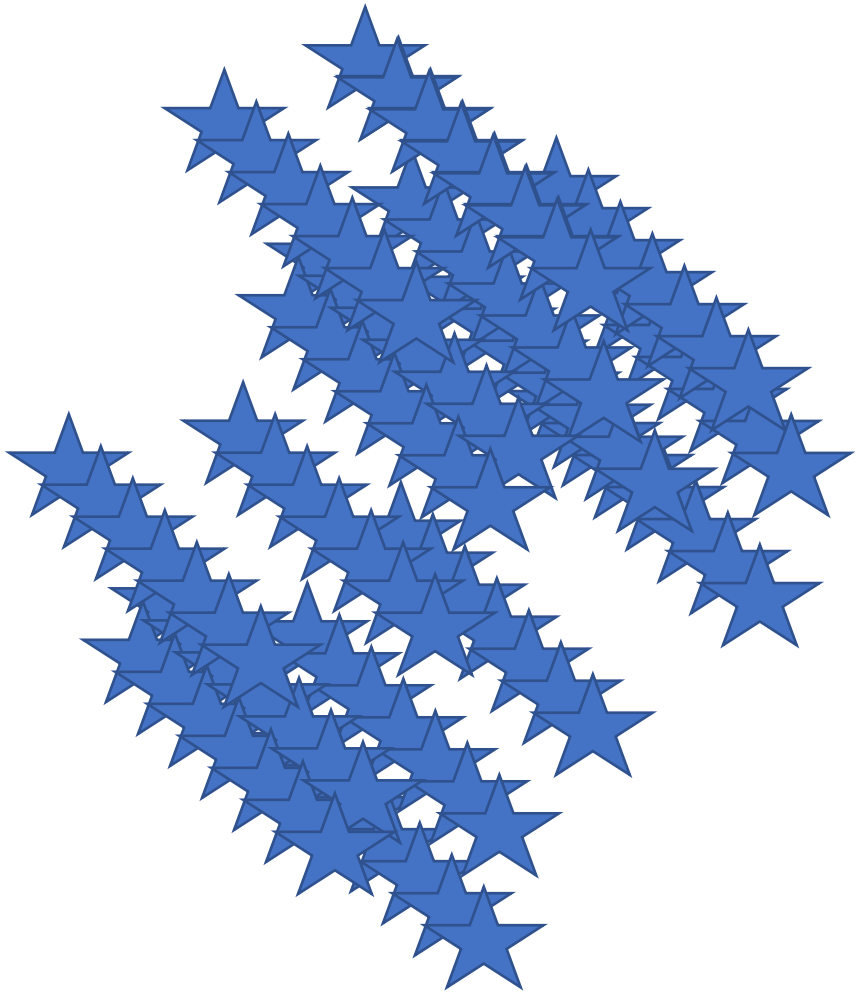
https://www.ncbi.nlm.nih.gov/books/NBK557848/#:~:text=Go%20to%3A-,Mechanism%20of%20Action,sucrase%2C%20maltase%2C%20and%20isomaltase.

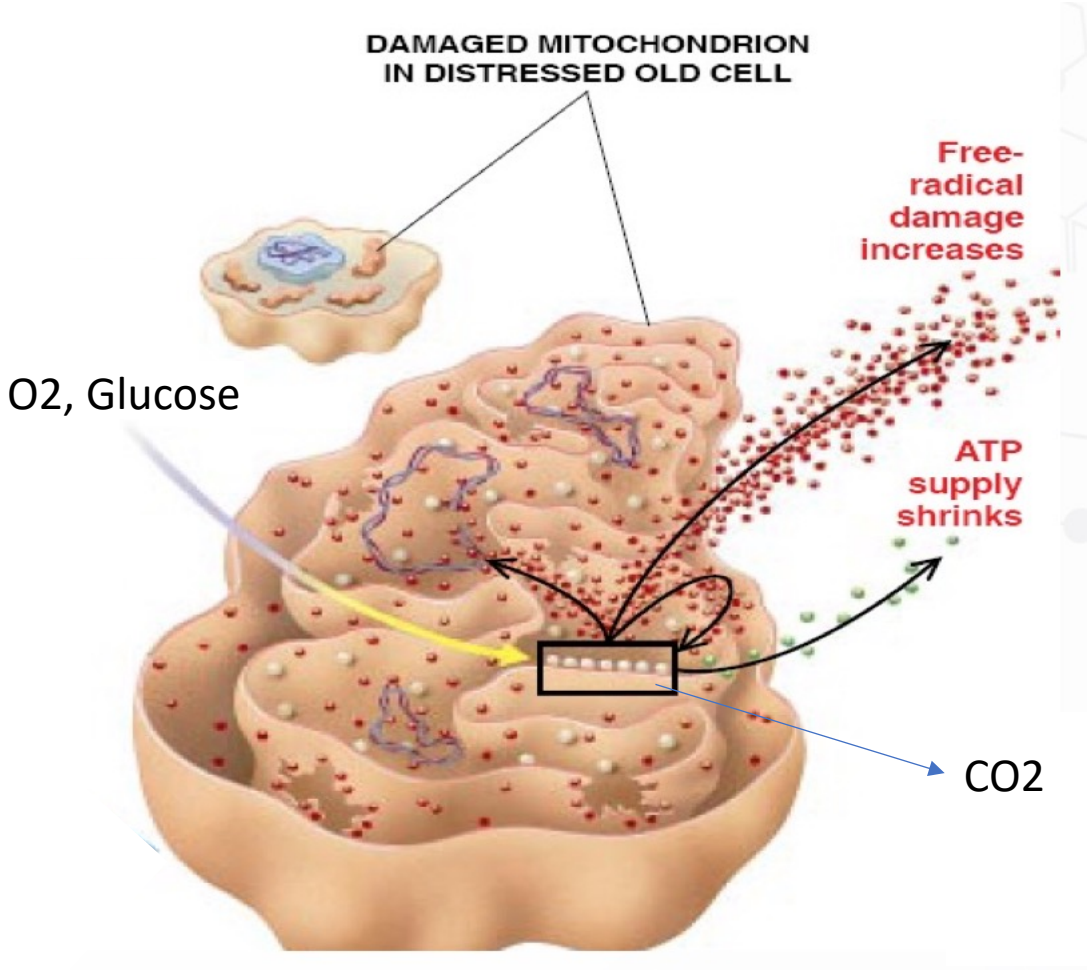
https://www.mdpi.com/2304-8158/10/8/1939#

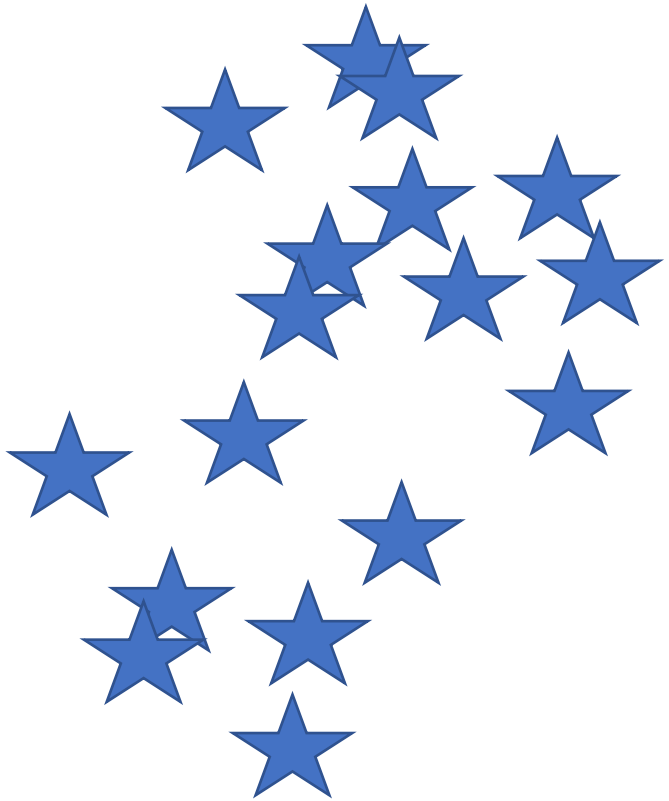
- ↑ Glucose uptake through induction of glycolysis/AMPK activation
- ↓ Adipogenesis through inhibition of PPARγ and C/EBPα function
- ↓ Glucose absorption by inhibition of α-glucosidase
- ↑ Pancreatic islet cell function via aldose reductase and MAPK inhibition and antioxidant activity
- ↓ LDL through activation of ERK and JNK pathways

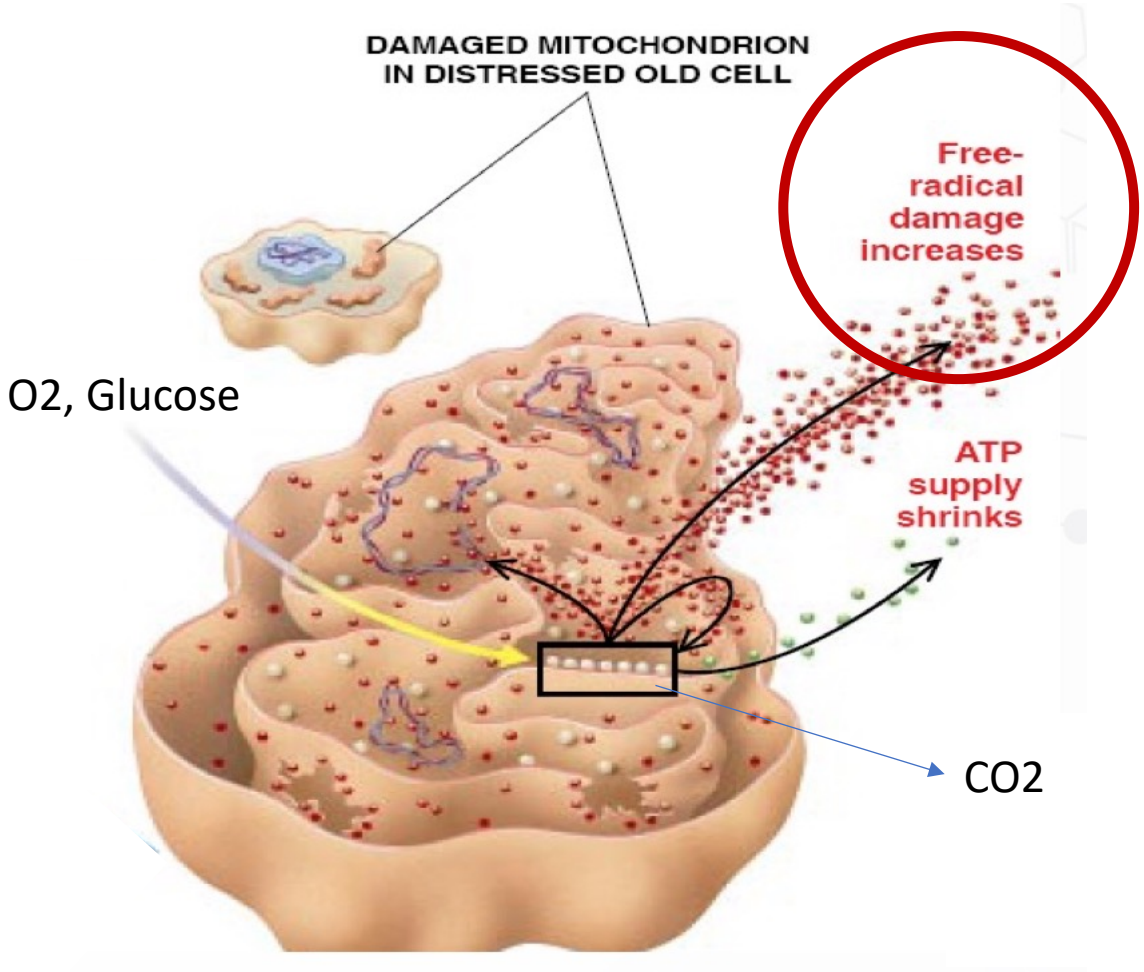


Yin J et al. *Acta Pharmaceutica Sinica B*. 2012;2(4):327-334. doi:10.1016/j.apsb.2012.06.003
Zhang Q et al. *Evid Based Complement Alternat Med*. 2011;2011:924851. doi:10.1155/2011/924851
Zhou L et al. *Metabolism*. 2007;56(3):405-412. doi:10.1016/j.metabol.2006.10.025

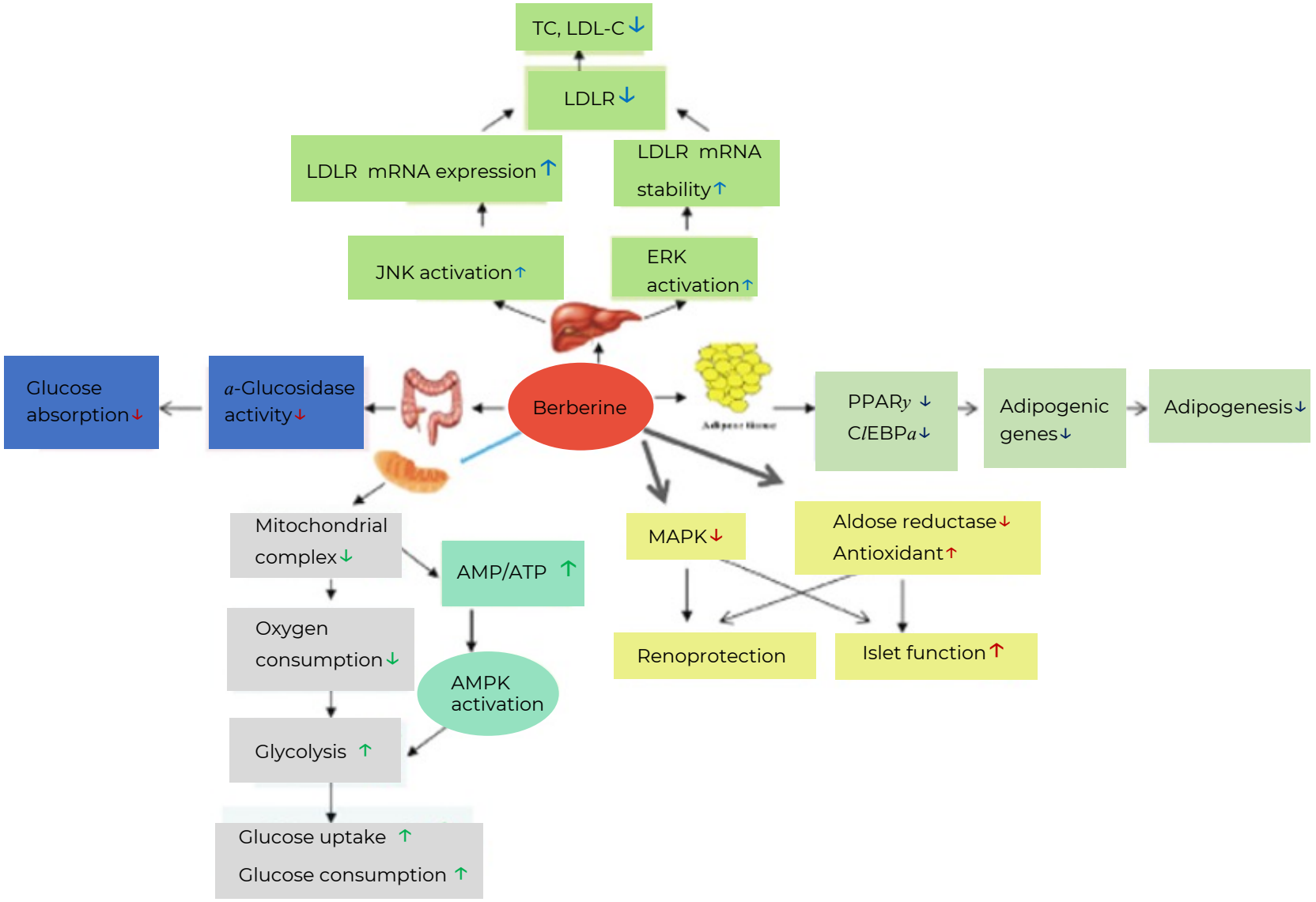



DAMAGED MITOCHONDRION
IN DISTRESSED OLD CELL
Free-
radical
damage
increases
ATP
supply
shrinks
O2, Glucose
CO2




DAMAGED MITOCHONDRION
IN DISTRESSED OLD CELL
Free-
radical
damage
increases
O2, Glucose
ATP
supply
shrinks
CO2

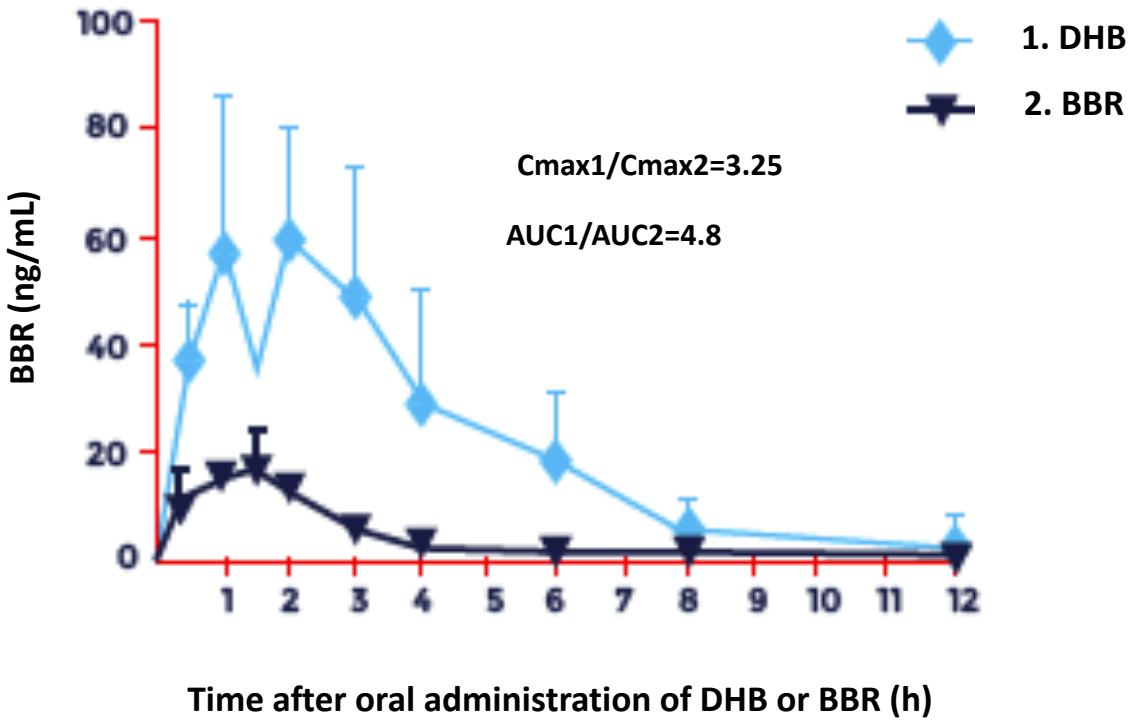
- ↑ Glucose uptake through induction of glycolysis/AMPK activation
- ↓ Adipogenesis through inhibition of PPARγ and C/EBPα function
- ↓ Glucose absorption by inhibition of α-glucosidase
- ↑ Pancreatic islet cell function via aldose reductase and MAPK inhibition and antioxidant activity
- ↓ LDL through activation of ERK and JNK pathways



Yin J et al. *Acta Pharmaceutica Sinica B*. 2012;2(4):327-334. doi:10.1016/j.apsb.2012.06.003
Zhang Q et al. *Evid Based Complement Alternat Med*. 2011;2011:924851. doi:10.1155/2011/924851
Zhou L et al. *Metabolism*. 2007;56(3):405-412. doi:10.1016/j.metabol.2006.10.025

Berberine Format Absorption

- Study explored the role of gut microbiota in berberine metabolism in rodents
- Blood level of berberine (BBR) exhibited values at 4.8- and 3.25-fold higher when treated with DHB
- Results indicated a higher intestinal absorption of DHB than BBR



Feng R et al. *Sci Rep*. 2015;5:12155. doi:10.1038/srep12155

Berberine Format Absorption

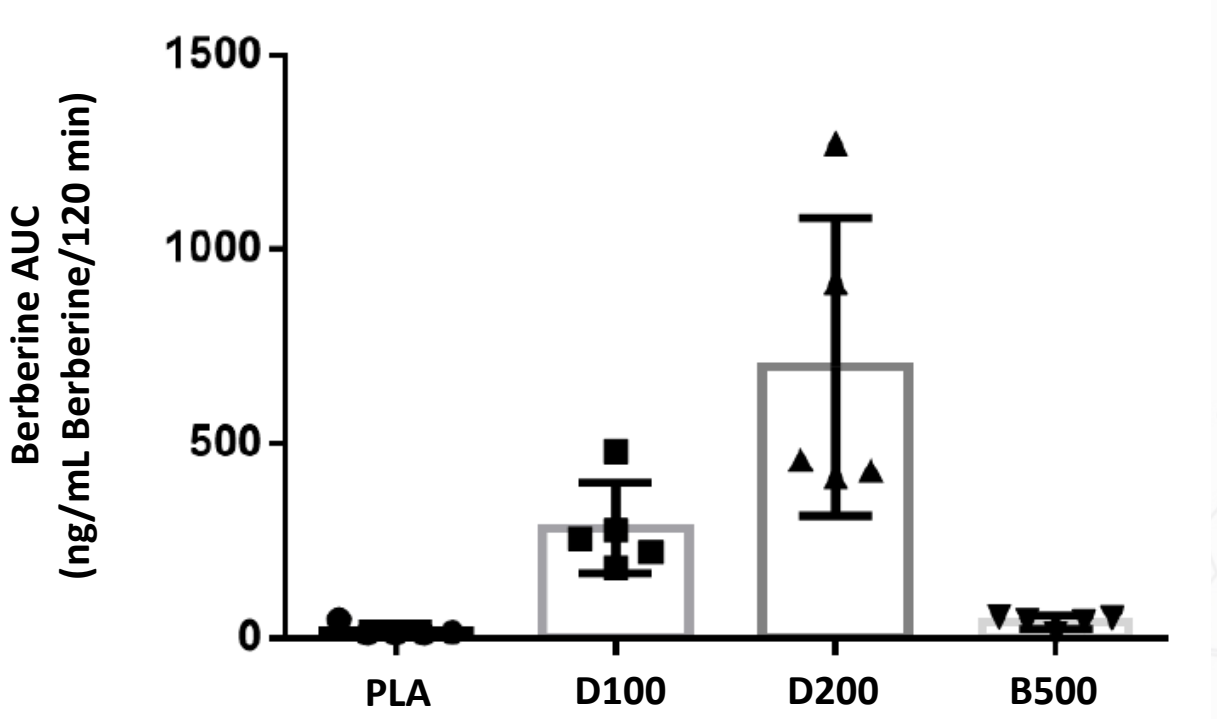
- Animal study investigated the mechanism of action in activating AMPK and the metabolic effect of DHB at lower doses than BBR
- Fed a high-fat diet and administered a nearly 5-fold increased dose of 560 mg/kg/d of BBR to establish the same effects demonstrated by DHB at 100 mg/kg/d
- The lower dose of DHB resulted in:
  - markedly reduced adiposity
  - improved glucose tolerance
  - an increase in insulin sensitivity

Conclusion: DHB delivers the beneficial metabolic effects of BBR in a more readily absorbed form at a lower dose.

Turner N et al. *Diabetes*. 2008;57(5):1414-1418. doi:10.2337/db07-1552

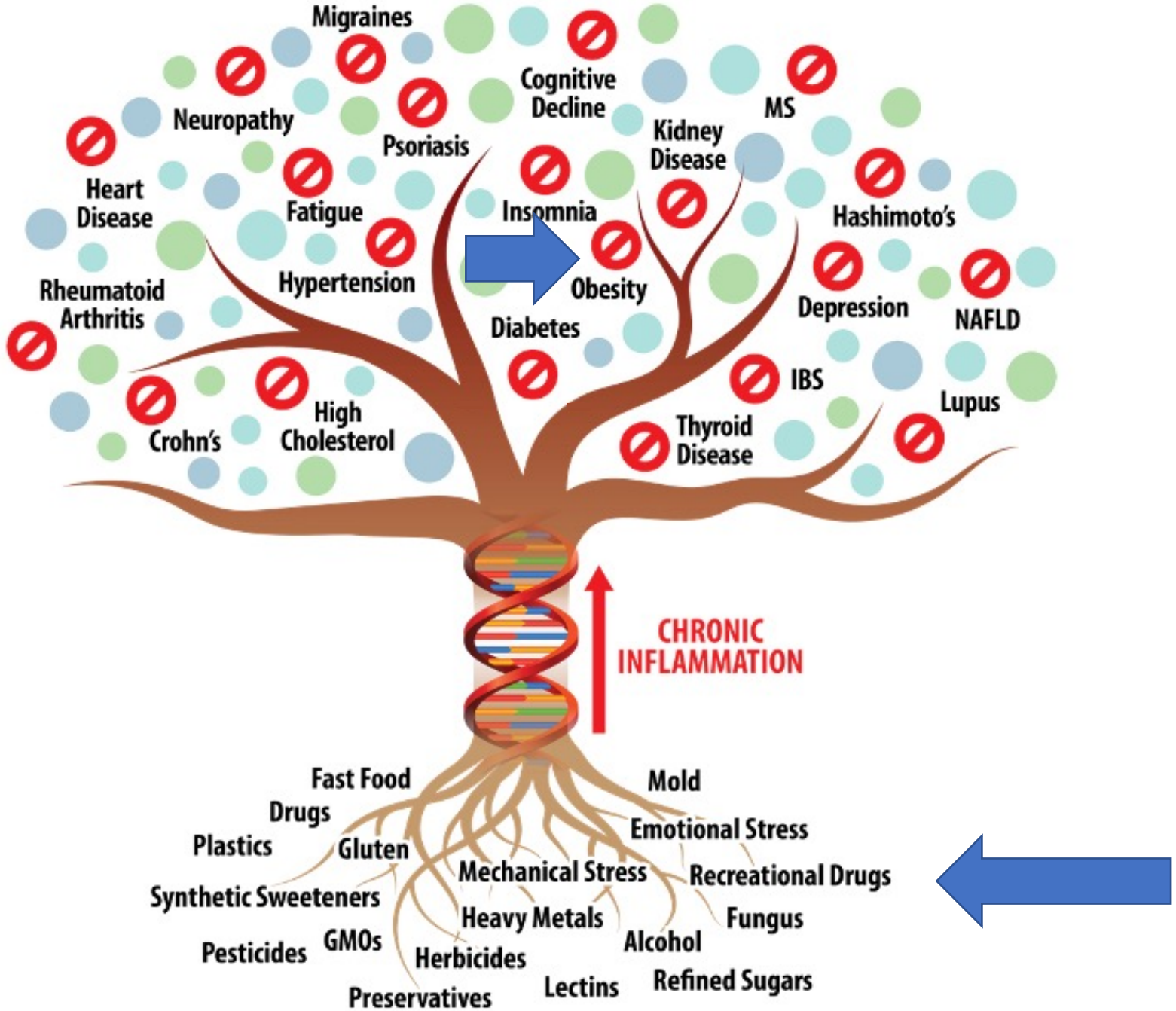
Berberine Format Absorption

- A randomized, double-blind, crossover pilot study compared a 4-dose protocol of BBR (500 mg) with DHB (200 mg and 100 mg)
  - DHB achieved higher peak berberine concentrations when compared with BBR
- An experimental pilot study investigated the use of BBR as a hypoglycemic agent
  - The dose of berberine required to improve biomarkers associated with glucose homeostasis had poor bioavailability and increased potential for GI distress
  - My Summary: DHB is the way to go.



Individual and aggregated mean values for berberine AUC by condition.

Moon J et al. *Nutrients*. 2021;14(1):124. doi:10.3390/nu14010124
Yin J et al. *Metabolism*. 2008;57(5):712-17. doi:10.1016/j.metabol.2008.01.013


Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Alcohol
Herbicides
Refined Sugars
Lectins
Preservatives

The Wedge Protocol