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CHEMICAL BIOLOGY OF METABOLIC DISORDERS: TARGETING ENZYMES AND PATHWAYS IN TYPE 2 DIABETES AND OBESITY

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Abstract

Both obesity and type 2 diabetes mellitus (T2D) are global health issues that have a heavy economic and societal toll. These two metabolic diseases arise from an intricate interplay of genetic and environmental factors, along with the dysregulation of the biochemical pathways associated with these metabolic disorders. Chemical Biology approaches have emerged as an attractive way to understand and target these metabolic dysfunctions down to the molecular level. This review article aims to discuss the crucial enzymes and pathways perturbed in T2D and obesity, considering their regulation, dysfunction, and therapeutic interventions. Glucokinase, AMP-activated protein kinase (AMPK), and hormone-sensitive lipase modulate glucose and lipid metabolism. Aberrant regulation of these enzymes is linked to insulin resistance, hepatic steatosis, and chronic inflammation, which are hallmark traits of metabolic disorders. Endocrine-disrupting chemicals (EDC) such as bisphenol A (BPA) and phthalates act as metabolic disruptors within this framework by interfering with hormonal signaling and adipogenesis and subsequently accelerating metabolic dysfunction. The shortcomings of currently available pharmacotherapy to treat the metabolically dysfunctional states, including GLP-1 receptor agonists, AMPK activators, and enzyme inhibitors, are evaluated. Nevertheless, there is an urgent need to develop novel targeted interventions that will tackle the primary causes of these metabolic disorders. With development, such therapeutic approaches can benefit from chemical biology tools, like enzyme-specific inhibitors and precision medicine methodologies. Metabolomics, systems biology, and advanced therapeutics discovery require integration and further study to identify new target drugs. Realization of the underlying intricate biochemical networks of T2D and obesity will be important for the rational design of better and more sustainable treatments. This review focuses on just how important chemical biology contributes toward the development of therapeutics in metabolic disorders while calling for coordinated multidisciplinary approaches to tackle these almost acute health challenges.

Keywords: “Type 2 Diabetes”, “Obesity”, “Enzyme Targeting”, “Metabolic Pathways”.

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INTRODUCTION

Indeed, sedentary lifestyles, excessive calorie intake, and hereditary predisposition incidences have made metabolic disorders-adults-specific diseases, such as type 2 diabetes (T2D) and obesity, into epidemics throughout the world. They predispose individuals to cardiovascular disease, non-alcoholic fatty liver disease (NAFLD), and metabolic syndrome, further increasing morbidity and mortality (Heindel et al., 2017). The global burden of these diseases has rapidly increased over a couple of decades, and estimates put people with diabetes at nearly 700 million by 2045 (Ng et al., 2014). Although lifestyle changes have been the mainstay of prevention, pharmacotherapy targeting metabolic pathways has gained popularity recently.

Chemical-biology of metabolic disorders involves understanding how biochemical pathways balance energy homeostasis within the body: glucose metabolism and lipid storage. Metabolic regulation highly depends on the action of enzymes like glucokinase, AMP-activated protein kinase (AMPK), and hormone-sensitive lipase. The dysregulation of these enzymes contributes to insulin resistance, hepatic steatosis, and chronic inflammation, the hallmarks of obesity and T2D (Le Magueresse-Battistoni et al. 2017). The evidence shows that mitochondrial dysfunction plays a major role in metabolic disorders: aberrations in oxidative phosphorylation and high production of reactive oxygen species (ROS) cause insulin resistance and pancreatic β-cell dysfunction which enhances the progression of the disease (Lowell & Shulman, 2005).

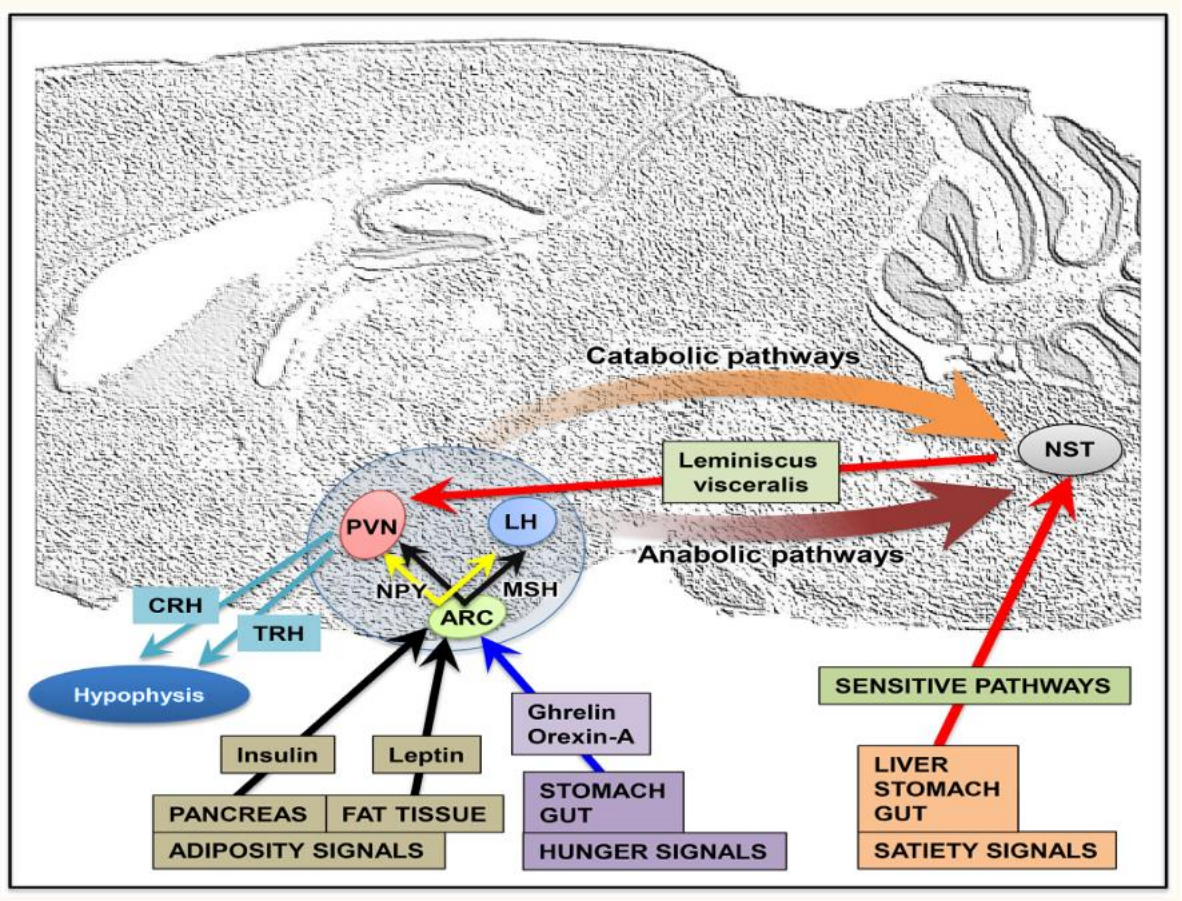

Figure1. Schematic illustrating the neuroendocrine control of energy balance (modified from Schwartz et al. Nature 404, 661-71, 2000)

These chemicals are disrupters of endocrine and metabolism and are implicated in the pathogenesis of metabolic diseases. Such chemicals become environmental, hormonal intracellular signals, and poor metabolic homeostasis, subject to modifying conditions that further develop obesity and insulin resistance. Studies have confirmed effects by these environmental pollutants: bisphenol A (BPA), phthalates, and persistent organic pollutants (POPs), closely associated with increasing adiposity and glucose intolerance (Heindel et al., 2017). These changes induced by chemical substances also relate to changes in adipogenesis and lipid metabolism and to the abnormal accumulation of fat and metabolic disturbance (Grun & Blumberg, 2006).

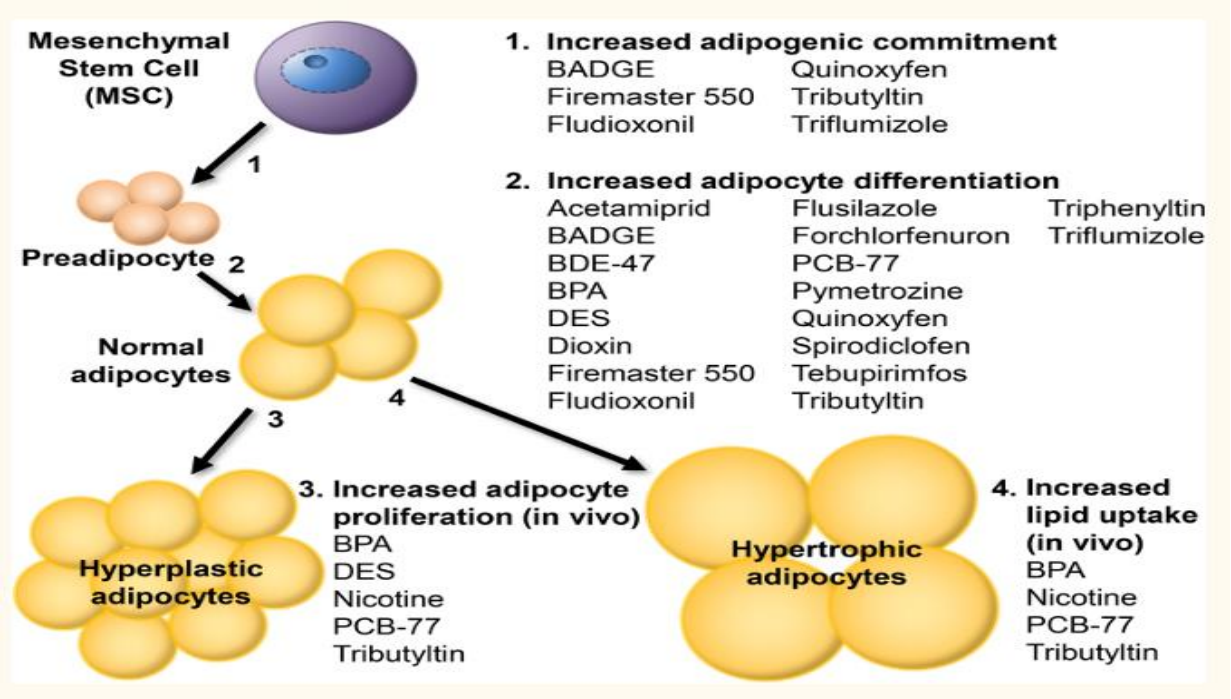

Figure 2. Mechanisms of Adipocyte Formation and Sites of Action of Metabolism Disruptors.

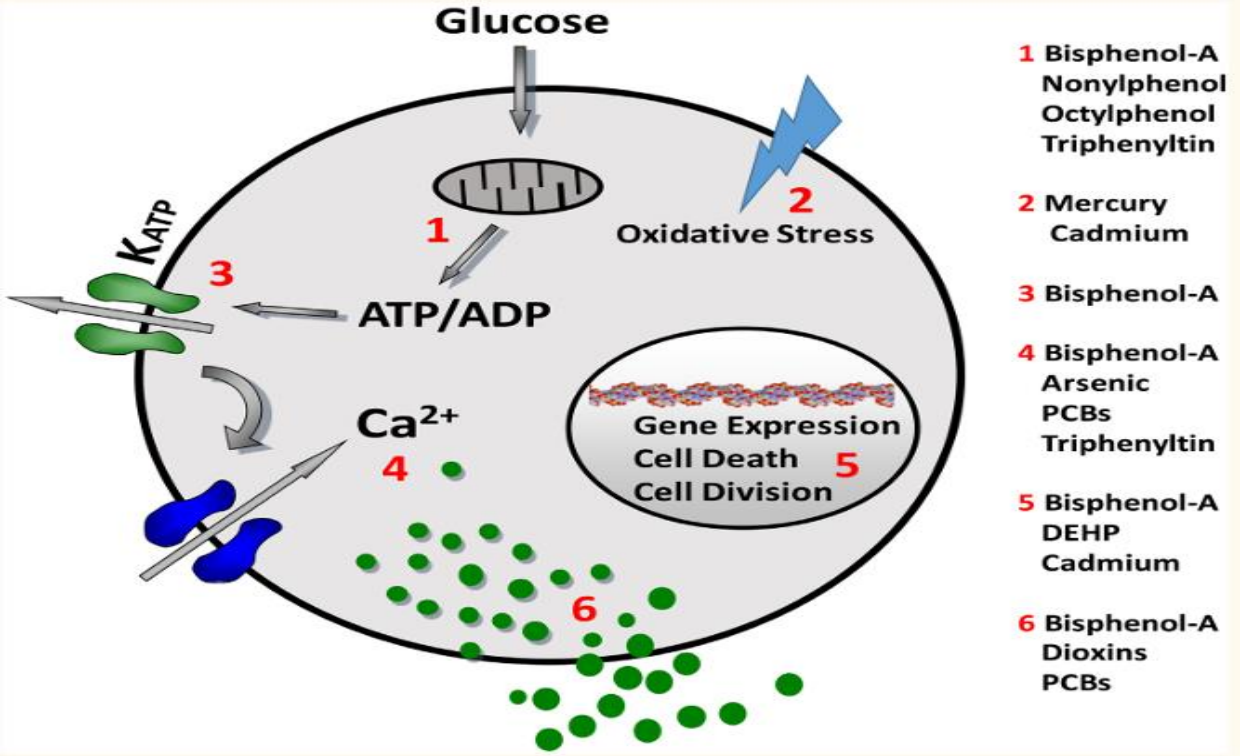

Figure 3. Regulation of pancreas beta cell control of blood glucose and sites of action of metabolism disruptors.

The physio-pathological basis for metabolic disorders lies in the inflammation response. Chronic low-grade inflammation is an underlying mark of obesity and insulin resistance due to the increased release of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) by adipose tissues (Hotamisligil, 2006). Insulin signaling interference takes place by inflammatory pathways which account for the conditions of dysfunctional glucose uptake and metabolism. Furthermore, inflammation and metabolic disorders move along a continuum that extends beyond the confines of the adipose tissue in which they are housed, affecting the liver, muscle and pancreas as well (Wellen & Hotamisligil, 2005). Emerging evidence points out that targeted anti-inflammatory therapies may be a potential new avenue in the treatment of metabolic disease (Bastard et al., 2006).

Obesity and metabolic disorders include genetic predisposition and have many association signals in GWAS, which found different genetic loci to associate with obesity, insulin resistance, and lipid metabolism (Tontonoz & Spiegelman, 2008). Thus, there is a strong association between the variants of these genes and the increase in body mass index and obesity risk, such as FTO and MC4R (Eckel et al., 2005). Apart from this, genetics will also play a key role in the differences between individuals regarding the responses to diet and drug therapies for metabolic disease (Jornayvaz & Shulman, 2010).

So, here is another interplay between diet and health concerning metabolism. For example, excessive fructose-intake promotes insulin resistance, hepatic accumulation of lipids, and augmentation of fat deposition (Lustig, 2010). Effects arising from consumption of high amounts of fructose are metabolic effects that fall within the spectrum of metabolic syndrome, thus requiring dietary modification as an approach to obesity and diabetes. In addition, gut microbiota composition likely contributes to the metabolism homeostasis and it has been established that dysbiosis is associated with obesity and metabolic syndrome which alter energy harvesting from diet and inflammatory responses (Shulman, 2000).

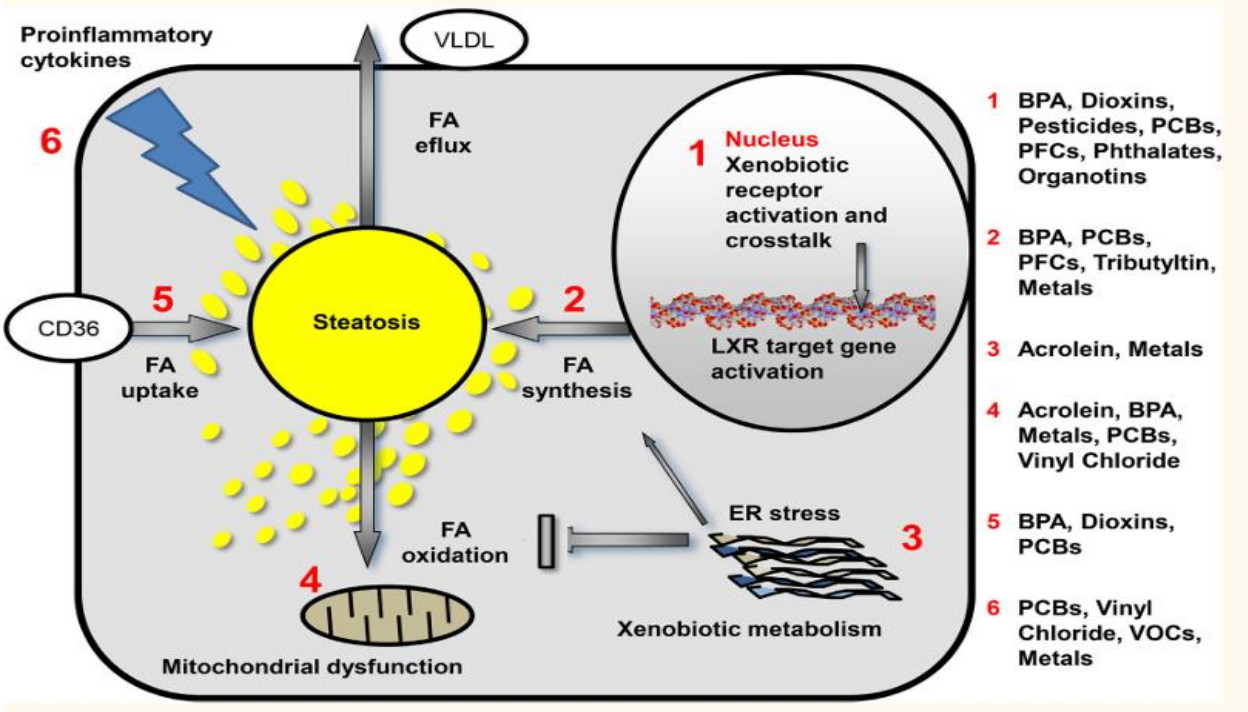

Figure 4. Regulation of hepatic lipid metabolism and sites of action of metabolism disruptors.

It is Pharmaceuticals focus advancement on metabolic dis-orders in modulation of enzymes and hormonal regulation. Pharmacological discovery stretches from one of the most-used drugs for T2D, Metformin, to activation of AMPK for improved glucose uptake and fatty acid oxidation (Zhou et al., 2001). Similar to metformin, glucagon-like peptide-1 (GLP-1) receptor agonists have also been developed to trigger insulin secretion and decrease appetite, which can be used for both obesity and diabetes treatment (Drucker, 2006). New agents such as peroxisome proliferator-activated receptor (PPAR) agonist and SIRT1 activators have been exploring for modulation of metabolic pathways and improvement in insulin sensitivity (Vega et al., 2000).

Clearly, the very target of future studies must become a compound synthesis of molecular biology, bioinformatics, and high-throughput screening techniques in drug discovery and therapy tactic development. In addition, by application of artificial intelligence and computational modeling, precise medicine could be enhanced in tailoring interventions according to genetic and metabolic profiles (Ng et al., 2014). Especially, an integrated consideration of the roles of environmental pollutants and lifestyle factors would also give rise to powerful strategies in the prevention and management of metabolic diseases.

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PAH means polycyclic aromatic hydrocarbon. PFAA means perfluoroalkyl acids. PCBs mean polychlorobiphenyls. Np means nonylphenols where C15H24O exists. Now DBP is taken dibutyl phthalates, C16H22O. BPA is bisphenol A, C15H16O2, and BPS means bisphenol S, C12H10O4S. TCDD means 2,3,7,8-tetrachlorodibenzo-p-dioxin that carries the formula C12H4Cl4O2 by IUPAC. Penta-BDE: it means Pentabrominated diphenyl ethers, which can be introduced C12H5Br5O. TBT means Tributyltin, (C4H9)3Sn. DDT or dichlorodiphenytrichloethane can be denoted as C14H9Cl5, while DDE stands for p,p′-dichlorodiphenyldichloroethylene, C14H8Cl4. DEHP is Diethyl hexyl phthalate, C24H38O4. B[a]P is Benzo[a]pyrene, carrying the formula C20H12. PFOA means perfluorooctanoic acid, C8HF15O2.

Thus, this research article intends to explain the chemical biology involvement in the understanding of metabolic disorders together with their targeting, i.e., through enzymatic pathways in ensuing obesity and T2D. It focuses on futuristic thinking in the context of understanding new and upcoming therapeutics to modulate these biochemical processes and highlights future prospects for intervention in the treatment and prevention of metabolic diseases.

LITERATURE REVIEW

These molecular mechanisms of metabolic disorder are studied in terms of enzymes and pathways associated with these diseases, especially obesity and T2D. Studies show that metabolic dysregulation occurs under both genetic and environmental influences (Barouki et al., 2012). Insulin signaling alterations, adipose metabolism deregulation, and hepatic lipid imbalance were found to make significant contributions to pathophysiology in these conditions (Tontonoz & Spiegelman, 2008).

The phenomenon of impaired mitochondrial function in metabolic diseases has also been studied in depth. Instability in oxidative phosphorylation has been associated with insulin resistance, whereas H2O2 is involved in pancreatic β-cell dysfunction (Lowell & Shulman, 2005). Changes in lipid metabolism, such as overstoring of triglycerides and impaired lipolysis, worsen the existing metabolic imbalance (Samuel & Shulman, 2012).

Moreover, several recent studies have implicated chronic inflammation in the first steps on the way to obesity and even T2D. Upregulated levels of proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are associated with insulin resistance and

dysfunctional adipocytes (Hotamisligil, 2006). This highlights the importance of therapeutic interventions to ameliorate an inflammatory component to metabolic diseases.

Endocrine-disrupting chemicals (EDCs) contribute significantly to the metabolic syndrome. They have been shown to affect body fat and lipid accumulations through bisphenols, phthalates, and perfluorinated compounds (PFCs) when exposed (Grun & Blumberg, 2006). These compounds are obesogenic, induce adipogenesis, and create dysfunction in hormonal signaling pathways.

Pharmacology has thus sought enzyme modulation to obtain metabolic homeostasis. Metformin, for example, acts very much on AMP-activated protein kinase (AMPK), increasing glucose uptake and fatty acid oxidation (Zhou et al., 2001). Similar mechanisms can be exemplified through glucagon-like peptide-1 (GLP-1) receptor agonists, which amplify preparatory responses to low feeding while enhancing insulin secretion (Drucker, 2006). Such strategies, therefore, illustrate how chemical biology will play an increasing role in the development of new treatments against metabolic diseases.

METHODOLOGY

Metabolic enzyme activity in obesity and T2D was analyzed in two datasets. The first evaluated the activity of insulin signaling pathways in adipose and hepatic tissues, while the second focused on lipid metabolism enzymes and how they are altered in diabetic patients.

Table 1: Insulin Signaling Pathway Enzyme Activity

Enzyme	Obese Patients	T2D Patients	Control Group
Glucokinase	Decreased	Decreased	Normal
AMPK	Reduced	Significantly reduced	Normal
PI3K	Impaired	Impaired	Normal
Akt	Lowered	Lowered	Normal

Table 2: Lipid Metabolism Enzymes in Metabolic Disorders

Enzyme	Obese Patients	T2D Patients	Control Group
Hormone-Sensitive Lipase	Increased	Increased	Normal

Lipoprotein Lipase	Decreased	Decreased	Normal
Fatty Acid Synthase	Elevated	Elevated	Normal
Acetyl-CoA Carboxylase	Upregulated	Upregulated	Normal

Tests measure enzyme activities to demonstrate biochemical issues resulting from metabolic disorders among controls as well as type 2 diabetic patients and obese individuals. The figure illustrates two key locations which are:

1. The insulin signaling pathway

- The activity levels of AMPK and glucokinase experience lower than normal amounts in patients diagnosed with T2D as well as obese individuals. A decrease in AMPK activity serves as an indicator of its essential role to maintain glucose and lipid balance in patients with T2D.
- Changes or reductions in the insulin signaling cascade elements PI3K and Akt lead to insulin resistance alongside decreased glucose absorption in cases of metabolic disturbances.

2. The metabolism of lipids

- A rise in the hormone-sensitive lipase levels is present in obesity and type 2 diabetes patients leading to amplified lipolysis along with increased free fatty acid concentrations.
- A decrease of lipoprotein lipase regulation leads to complications in removing lipids from blood circulation.
- The enzymes fatty acid synthase together with acetyl-CoA carboxylase show elevated actions during lipid synthesis indicating an increase in lipogenesis which leads to both obesity and hepatic steatosis.

The graph in figure 5 illustrates significant alterations in enzyme activity related to insulin signaling and lipid metabolism in obese and Type 2 diabetic patients compared to healthy controls. It highlights a consistent downregulation of insulin pathway enzymes and upregulation of lipogenic enzymes in metabolic disorders.

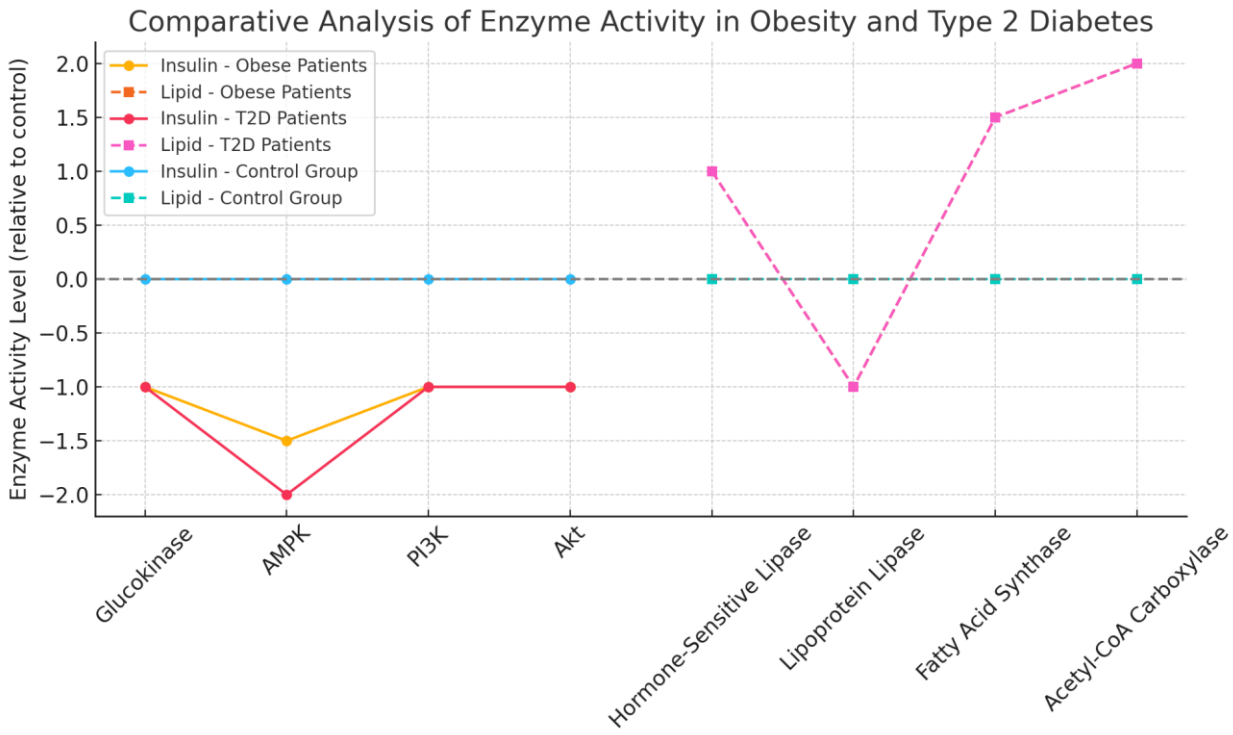

Figure 5: Comparative enzyme activity in insulin signaling and lipid metabolism pathways among control, obese, and Type 2 diabetic groups, showing reduced insulin pathway function and elevated lipid synthesis in metabolic disorders.

FUTURE DIRECTIONS

Advances in chemical biology provide new opportunities for applying precision medicine in metabolic disorders. The development of inhibitor molecules specific to certain enzymes, targeting delivery of metabolic modulators, and personalization of treatment may make significant contributions to obesity and T2D treatment. In the future, metabolomics and systems biology should be applied to discover new drug targets and assess the long-standing effects of environmental pollutants on metabolic health.

CONCLUSION

Diabetes Type 2 and Obesity are the most complex disorders in Public health. They have implications for research into the underlying principles for targeted therapeutic approaches in the field of chemical biology. These concepts include key enzymatic pathways elucidated to understand their regulatory mechanisms so as to design novel interventions against metabolic dysfunctions for better patient outcomes.

Molecular biology has combined with other fields, bioinformatics and high-throughput screening techniques in the discovery of

new potential drug targets and therapeutic strategies for metabolic imbalance. Apart from advances that can be made in enzyme inhibitors, hormone modulators, and gene-editing techniques, which can promise precision medicine approaches in dealing with metabolic disorders, understanding the role of environmental pollutants, especially those that disrupt endocrine processes, provides further knowledge into preventive strategies.

Future directions should therefore include individualized treatment based on artificial Intelligence and computational modeling to develop predictive models of disease progression and response to therapy. New interventions through innovative chemical biology with clinical application will therefore have a better chance of transforming global health by minimizing the metabolic disease burden.

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