

## Metabolic Flexibility in Health and Disease as an Adaptation to Energy Resources and Requirements

Maarten Wust

Department of Endocrinology and Genetic Metabolic Diseases

### Abstract (Limit: 600 Words)

Metabolic flexibility is the ability to alter metabolism efficiently based on substrate supply and requirement through substrate sensing, trafficking, storage, and utilisation. The breadth and depth of metabolic flexibility, as well as its impact on health and disease, are discussed in this article. Metabolic flexibility is required to maintain energy balance throughout periods of caloric excess or restriction, as well as periods of low or high energy demand, such as during exercise. By communicating via endocrine cues, the liver, adipose tissue, and muscle regulates systemic metabolic flexibility and manage nutrition sensing, absorption, transport, storage, and expenditure. Metabolic flexibility is based on the configuration of metabolic pathways, which is controlled by major metabolic enzymes and transcription factors, many of which interact closely with mitochondria. Disrupted metabolic flexibility, also known as metabolic inflexibility, is linked to a number of diseases, including metabolic syndrome, type 2 diabetes, and cancer. Metabolic flexibility is influenced by a variety of factors, including food composition and eating frequency, exercise training, and the use of pharmacological agents, all of which will be described here. Finally, we address key developments in metabolic flexibility research, as well as medical prospects and translational implications. Human

physiology developed under periods of extreme energy supply and demand. The ability to govern energy metabolism for optimal substrate storage and utilisation during conditions of either food glut or famine, and periods of either rest or increased energy demand has become ingrained in the human body as a result of coping with these fluctuations. Metabolic flexibility is the ability to adapt metabolism efficiently based on demand or supply (1). In general, moderate amounts of carbohydrates, fatty acids, and amino acids are well tolerated by the human body. However, the contemporary era is marked by unparalleled levels of food supply (2). This near-constant intake of calorie-dense processed foods, combined with physical inactivity, lowers metabolic flexibility and directly impedes it. This is produced by substrate competition and metabolic insensitivity, which causes nutrition sensing to be skewed, substrate switching to be dulled, and energy balance to be disrupted (4). Importantly, this metabolic inflexibility may be at the root of the epidemic changes in metabolic disease that afflict people of all ages and put a strain on health-care systems.

### Importance of Research (Limit: 200 words)

Substrate sensing, trafficking, storage, and usage are required to maintain energy homeostasis, which is based on substrate availability (push concept) and energy

demand (pull concept). When Saltin and Gollnick studied the metabolic changes of skeletal muscle to exercise in 1983, they discovered metabolic plasticity (or adaptability). researchers developed the term metabolic flexibility in 1999 when they researched fuel choices in skeletal muscle in lean and obese people after an overnight fast. They discovered that lean people's skeletal muscle had a remarkable ability to change fuel preferences to fasting and insulin infusions, and therefore were labelled as metabolically flexible. Insulin-resistant obese people, on the other hand, showed a lower reliance on fatty acid oxidation than lean persons, with no evidence of enhanced fatty acid oxidation after fasting or decreased fatty acid oxidation following insulin infusion. These patients were labelled "metabolically inflexible" because of their poor reactions to metabolic challenges (9). More recent research found that slim persons with enough metabolic flexibility were able to increase fatty acid oxidation (FAO) at the expense of glucose when fed a high-fat diet, whereas obese people were not (10). Lean people also had higher expression of genes involved in fatty acid transport and oxidation, compared to obese people who had little or no change.

#### Biography (Limit: 200 words)

Maarten Wust is working as a researcher in the Laboratory of Genetic Metabolic Diseases, Academic Medical Center, Amsterdam, Netherlands He completed his graduation from Academic Medical Center, Amsterdam, Netherlands and Amsterdam Movement Sciences, Academic Medical Center. He has published several research papers

#### University Information (Limit: 200 words)

The Academic Medical Center or AMC, is the university hospital affiliated with the University of Amsterdam. It is one of the largest and leading hospitals of the Netherlands, located in the Bijlmer neighborhood in the most south-eastern part of the city of Amsterdam. AMC consistently ranks among the top 50 medical schools in the world.



#### References (15 – 20)

1. [Olson KA, Schell JC, Rutter J. Pyruvate and metabolic flexibility: illuminating a path toward selective cancer therapies. \*Trends Biochem Sci.\* 2016;41\(3\):219–230.](#)
2. [Speakman JR. Evolutionary perspectives on the obesity epidemic: adaptive, maladaptive, and neutral viewpoints. \*Annu Rev Nutr.\* 2013;33\(1\):289–317.](#)
3. López-Otín C, Galluzzi L, Freije JMP, Madeo F, Kroemer G. Metabolic control of longevity. *Cell.* 2016;166(4):802–821.
4. Muoio DM. Metabolic inflexibility: when mitochondrial indecision leads to metabolic gridlock. *Cell.* 2014;159(6):1253–1262.