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Effekt von Flavonoiden auf die Glukoseaufnahme durch Adipozyten

Effect of flavonoids on adipocytic glucose uptake

Melina Claussnitzer*

Abstracts

Adipozyten sind ein bedeutender Wirkungsort von Insulin und tragen auf diese Weise bedeutend zur Regulation der Glukosehomöostase bei. Dieser Prozess wird hauptsächlich durch die Translokation des insulinempfindlichen Glukosetransporters GLUT4 vermittelt. Eine beeinträchtigte GLUT4 Translokation spielt eine entscheidende Rolle in der Pathogenese der Insulinresistenz, als eines der anfänglichen Ereignisse während der Entwicklung des Typ 2 Diabetes mellitus.

Der insulinstimulierte Glukosetransport in Adipozyten kann nicht nur durch eine Beeinträchtigung der Insulinsignalkaskade, sondern auch durch eine direkte Interaktion mit dem Glukosetransporter GLUT4 beeinflusst werden. Flavonoide, die zu der Gruppe der Polyphenole gehören, üben eine Vielzahl biologischer Effekte aus. Nach neuestem Kenntnisstand inhibieren gewisse Flavonoide die GLUT4-vermittelte Glukoseaufnahme in Adipozyten. Angesichts der geringen Bioverfügbarkeit der meisten Flavonoide ist dieser möglicherweise schädliche Effekt auf die Glukosehomöostase jedoch als vernachlässigbar zu werten.

Stichwörter: Adipozyt, Insulin, Glukosehomöostase, Glukosetransporter, Flavonoide

Adipocytes are a major site of insulin action, being thereby contributors to the regulation of whole-body glucose homeostasis. This process is mainly mediated by translocation of the insulin-responsive glucose transporter GLUT4. An affected GLUT4 translocation plays a crucial role in the pathogenesis of insulin resistance as one of the earliest events during the development of type 2 diabetes.

Inhibition of insulin-stimulated glucose uptake in adipocytes can not only occur via an impairment of the insulin signalling cascade, but also extracellular via direct interaction with the glucose transporter GLUT4. Flavonoids are a group of polyphenolic compounds which are known to exert a variety of biological effects. Evidence is emerging that some flavonoids appear to affect GLUT4-mediated glucose uptake in adipocytes. However, this potential harmful effect in glucose homeostasis is assessed to be negligible regarding the low bioavailability of flavonoids.

Keywords: Adipocyte, insulin, glucose homeostasis, glucose transporter, flavonoids



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ROLE OF ADIPOSE TISSUE IN GLUCOSE HOMEOSTASIS

Glucose is a fundamental source of energy for all eukaryotic cells. Several mammalian tissues, notably the brain are primarily dependent on glucose. Finely tuned regulatory systems have evolved in mammals to maintain remarkably stable plasma glucose concentrations regardless of large fluctuations in food intake and physical activity. This requires the concerted actions of a variety of tissues. In fasting state, low insulin levels combined with elevated levels of glucagon, catecholamines and corticosteroids promote gluconeogenesis and glycogenolysis by the liver resulting in a net glucose output from the liver. In contrast, after huge caloric ingestion elevated glucose levels are rapidly reversed to normal. Following an exogenous glucose load, the release of incretins into the circulation and elevated levels of plasma glucose trigger pancreatic β -cells to secrete insulin into the blood stream.

Insulin suppresses the hepatic gluconeogenesis and glycogenolysis and promotes glucose disposal by facilitating the net glucose uptake in adipose tissue and skeletal muscle. As a result, the whole-body energy stores are replenished by lipogenesis in the adipose tissue and production of glycogen in the muscle and the liver. This complex interplay between glucose absorption from the intestine, production and output by the liver, and metabolism and storage by peripheral tissues is exquisitely balanced such that plasma glucose concentrations are tightly controlled in a narrow range between 4 and 7 mM. The storage of energy is of particular importance for the body as it is impractical for organisms to meet this need by supplying a constant external source of calories.

The specialized white adipose tissue has evolved to meet the ongoing requirement for energy. White adipocytes are able to store excess calories in the form of triacylglycerol, constituting up to 85 % of tissue weight (Figure 1).

When cells require energy, such as during periods of fasting or exercise, these needs are largely met by fatty acids formed from lipolysis of stored triacylglycerol. In the last decade, adipose tissue has been recognized as an active organ secreting a variety of factors called adipokines into the circulation thereby exerting multiple effects (Hauner et al., 1998). Accordingly, adipose tissue is integrated in the complex network of energy homeostasis and thereby implicated in the metabolic and physiological control of the whole body, particularly with regard to glucose homeostasis.

The basic glucose transport into white adipocytes is mainly mediated by the basal glucose transporter GLUT1. Glucose transport following insulin stimulation in contrast involves the glucose transporter GLUT4 (Cushman and Wardzala, 1980). GLUT4 displays the unique characteristic of a mostly intracellular disposition in the absence of insulin that is instantaneously redistributed to the plasma membrane in response to insulin.

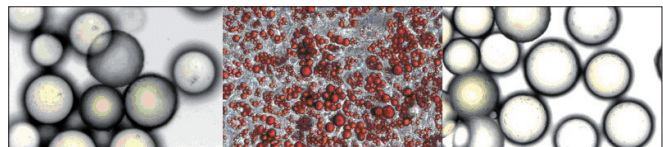


Figure 1: Mature human adipocytes and differentiated mouse 3T3-L1 adipocytes (Oil-Red-O stain).

The majority of postprandial glucose disposal occurs in skeletal muscle in vivo (Goodyear and Kahn, 1998). By contrast, the adipose tissue accounts for only a small fraction of 10 – 15 % of glucose uptake after ingestion of dietary carbohydrates. However, the insulin-stimulated increase of glucose uptake in adipose tissue is critical for maintaining normal whole-body

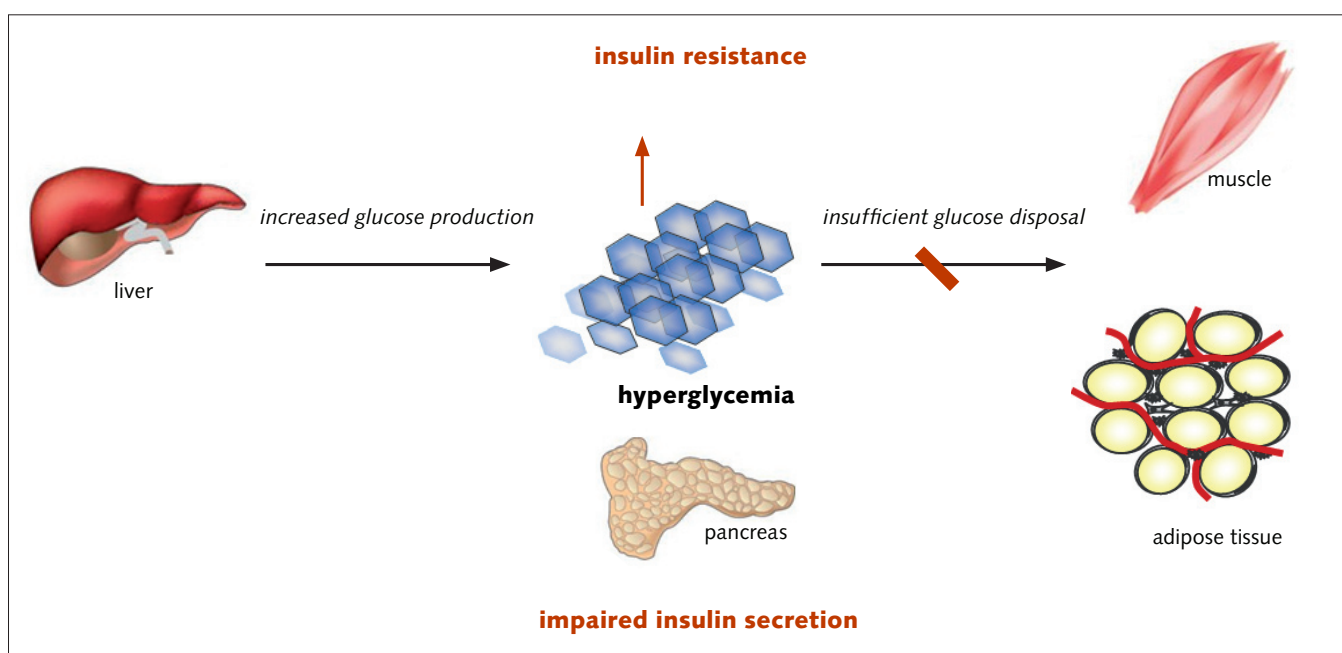


Figure 2: Hyperglycemia results from an impaired insulin secretion from pancreatic β -cells and insulin resistance in liver, skeletal muscle and adipose tissue.

Structure of flavonoids

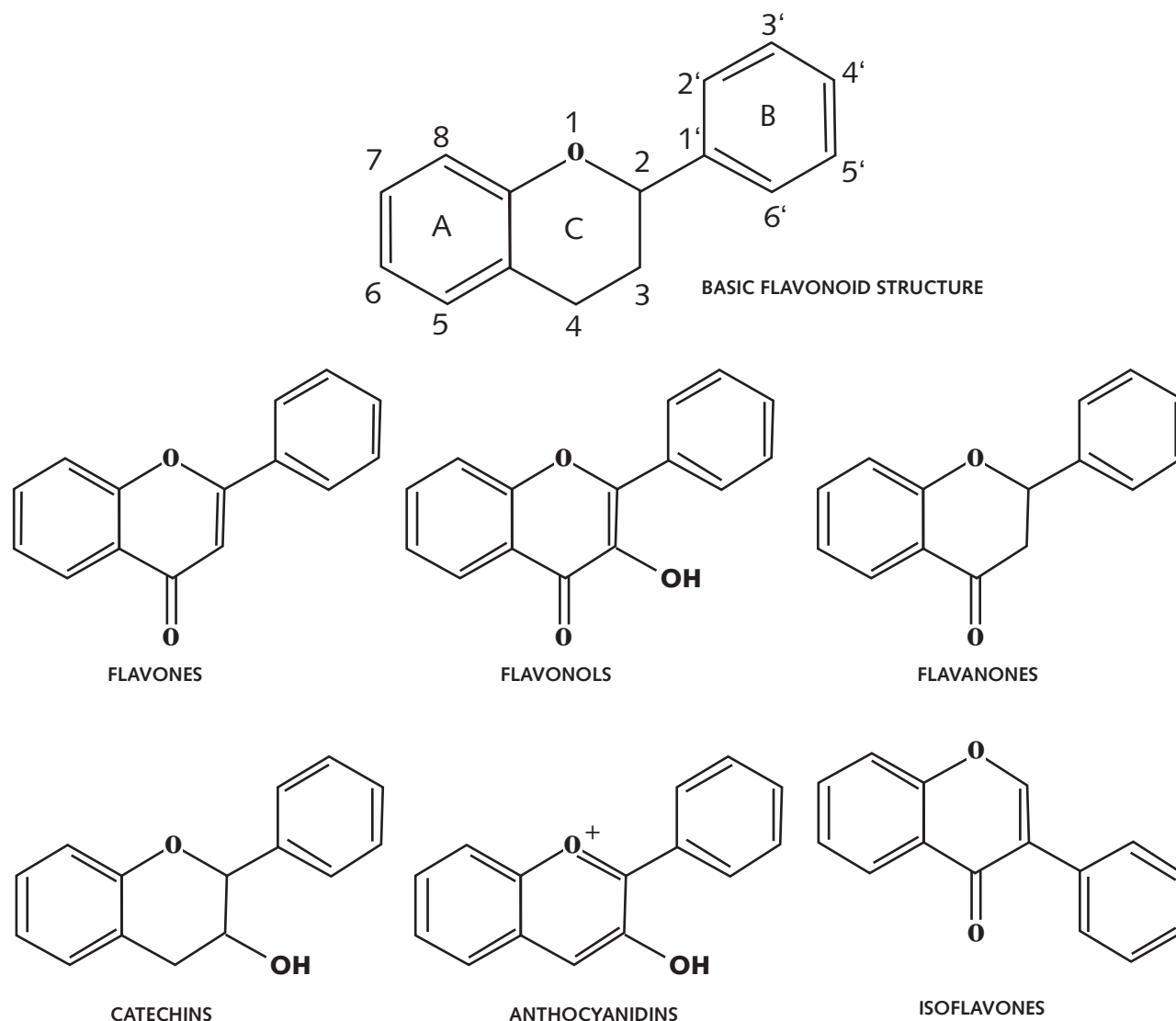


Figure 3: The basic structure of flavonoids is composed of benzopyran and benzene groups. Based on common structural features, flavonoids are divided in flavones, flavonols, flavanones, catechins, anthocyanidins and isoflavones.

glucose homeostasis. In insulin resistant states, GLUT4 translocation is impaired and the amount of GLUT4 in adipose tissue is reduced (Figure 2). Mice with an adipocytic GLUT4 ablation display a phenotype of insulin resistance in fat tissue as well as in muscle and liver, resulting in a marked impairment of glucose tolerance and hyperinsulinemia (Abel et al., 2001). Long term changes of GLUT4 abundance on the cell surface of adipocytes due to obesity might provoke systemic changes of glucose disposal in vivo. Thus, when adipocytes are fully loaded with triglycerides, they reduce GLUT4 expression and produce several signals causing decreased insulin-dependent glucose uptake thereby preventing cells to store more fat (Powell, 2007). However, the increased glucose levels trigger an insulin resistant state as well as problems associated with hyperglycaemia including renal failure, blindness, neuropathy, and cardiovascular disease. Thus, GLUT4-mediated glucose uptake in

adipose tissue emerges as a critical mechanism for maintaining whole-body glucose homeostasis.

FLAVONOIDS

Flavonoids are a group of polyphenolic compounds which are widely distributed in plants, fulfilling diverse functions such as pigmentation of flower petals, attraction of insects for pollination or fruit and seed dispersal. These compounds share a common chemical structure consisting of two phenolic rings linked through a heterocyclic pyran or pyrone ring system (Figure 3). The interlinkage between the aromatic ring and the heterocyclic ring system as well as the degree of oxidation in the heterocyclic C-ring are the basis of the classification of flavonoids into six subgroups including flavones, flavonols, flavanones, isoflavones, catechins or flavanols and anthocyanidins (Hav-

teen, 1983). Upon ingestion, flavonoids are considered to pass through the small intestine, which can act as an effective absorption site for flavonoid glycosides. Furthermore, specific glycosidases on the cellular membrane of enterocytes may contribute to hydrolysis followed by uptake of aglycones. In the course of detoxification, the flavonoid aglycones are subject to O-methylation, glucuronidation and sulfation in the liver. Only a small part of the flavonoid metabolites circulates, with flavonoid glucuronides being the major metabolites present in the systemic circulation.

Flavonoids are recognized as dietary constituents with a variety of biological effects and health-enhancing properties such as preventing atherosclerosis and cancer, lowering of blood cholesterol levels and improving bone strength. In recent years, there is growing interest in the therapeutic applications of flavonoids and other naturally occurring polyphenols for the treatment and prevention of diseases in humans. The biological effects of flavonoids are often attributed to their antioxidant properties. However, flavonoids can also display pro-oxidant activities, after donating electrons either by antioxidant action, enzymatic oxidation or autooxidation. In fact, growing evidence suggests that many of the biological effects of flavonoids are related to their ability to modulate cell signaling pathways based on their molecular interactions with specific enzymes like protein-tyrosine kinases phosphodiesterases, phosphatases and others.

Evidence is emerging that some flavonoids appear to modify glucose uptake in adipocytes. Certain flavonoids are known to modulate glucose transport through interaction with the insulin pathways at different levels. Thus, the soybean-derived phytoestrogen genistein, which is commonly used as a tyrosine kinase inhibitor, was found to affect insulin signaling pathways downstream of the insulin receptor, thereby inhibiting glucose uptake in rat adipocytes (Smith et al., 1993). Inhibition of insulin-stimulated glucose uptake in adipocytes can not only occur by an impairment of the insulin induced phosphorylation cascade, but also extracellular via direct interaction with the glucose transporter.

In fact, apart from the interaction of flavonoids with enzymes of certain signalling pathways, evidence is emerging that several flavonoids affect glucose and vitamin C transport in several cell types like erythrocytes and gut epithelial cells via direct interaction with the facilitative glucose transporters (GLUTs) and the sodium-dependent glucose transporters (SGLTs) (Kwon et al., 2007; Kottra and Daniel, 2007). The adipocytic basal glucose transporter GLUT1 and the insulin-responsive glucose transporter GLUT4 have also been shown to interact with flavonoids like quercetin (onions), myricetin, catechin-gallate (black tea) and genistein (unpublished data) in relatively high concentrations.

Given the role of adipocytic glucose uptake in whole-body glucose homeostasis, an impaired glucose transport in the presence of high concentrations of the mentioned flavonoids might have an adverse effect in the pathogenesis of type 2 diabetes. However, studies of bioavailability have shown that the concentrations of intact flavonoids in human plasma rarely exceed 1 μM after the consumption of 10 – 100 mg of a single compound (Conquer et al., 1998). Therefore, supraphysiological concentrations of the respective flavonoid are required for an inhibitory effect. The potentially harmful effect of mentioned flavonoids on blood glucose concentration is judged to be negligible.

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