Flavonoids are polyphenolic secondary plant metabolites with a wide range of biological activities. There is an increasing awareness of the role of flavonoids as epidemiological studies suggest that consumption of flavonol- and isoflavone-rich diets may decrease the risk of developing coronary heart disease and certain cancers.

Apart from some fermented foods and tea, where flavonoid aglycones are present, most of the dietary flavonoids are O-glycosides, mainly with D-glucose and in this form are ingested.

As a rough estimate, the total daily intake of polyphenols is between 150 and 1000 mg.

The paper is focused on the flavonoid (especially quercetin-related) metabolism. The processes involved are deglycosylation, transfer into enterocytes, glucuronidation, transport to liver via hepatic vein, or resecretion into intestinal lumen, further conjugation reactions in liver, enterohepatic recirculation, biliary and urinary excretion, metabolism by colonic microflora.

Key words: flavonoids, quercetin, absorption, metabolism, secretion.

Introduction

Flavonoids are polyphenolic secondary plant metabolites with a wide range of biological activities. There is an increasing awareness of the physiological role of flavonoids in human as epidemiological studies suggest that consumption of flavonoid-rich diets may decrease the risk of developing coronary heart disease and certain cancers. Apart from some fermented foods as tempeh, wine and tea, where flavonoid aglycones are present, most of dietary flavonoids are O-glycosides, mainly with D-glucose and in this form are ingested.

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As a rough estimate, the total daily intake of polyphenols is between 150 and 1000 mg [1]. However, the wide range of results is due to diversity of dietary habits and methodology of estimation applied. Out of all dietary flavonoids quercetin is one of the consumed in the highest amounts. From different foods onions are especially rich in quercetin. Most commonly consumed yellow varieties contain quercetin glucosides in amounts about 600 mg/kg expressed as free quercetin.

Once ingested, food has to undergo a number of processes within alimentary tract leading to absorption of spectrum of its components. Part of them, with flavonoids, accounted to xenobiotics when absorbed are subjects to intensive multi-step metabolism significantly changing their physiological properties.

**Alimentary tract**

The epithelium-lined alimentary tract can be conceptualised as a tunnel through the body, and the wall of the alimentary canal as the interface between the external environment and the circulatory system [5]. To enter the body, the nutrient requires to traverse the epithelium.

There are several factors affecting flavonoid absorption, like the presence or absence of glycosylation on hydroxyl groups, quality of sugar moiety attached, plant/food matrix, interactions with food components, micelles, and emulsifiers. The tissue distribution of β-glucosidases, enzymes hydrolysing flavonoid glucosides, affects the site of flavonoid uptake, too.

**Oral cavity**

β-Glucosidases in the mouth can be of endogeneous and/or microbial origin. Although flavonoid deglycosylation in saliva is unlikely and has not been reported yet, phenolics can undergo oxidation in the oral cavity.

**Stomach**

Non-enzymatic deglycosylation of flavonoids in the body, such as gastric acid hydrolysis, does not occur. Piskula et al. [14] and Crespy et al. [2] reported rapid absorption of flavonoid aglycone from rat stomach after its in situ administration. Related glucosides, were not deglycosylated nor absorbed either in this experiment. Contrary to the above findings, partial flavonoid deglycosylation was reported [13] to occur in rat stomach after flavonoid glycosides (of quercetin, kaempferol, isorhamnetin, apigenin, luteolin and chrysoeriol) were administered in aqueous suspension, extracted from parsley. This was probably due to β-glucosidase activity of bacteria colonising the rat forestomach. Human deglycosylation has not been reported.
Small intestine

The epithelium of the small intestine is located at a strategic interface as the intestinal lumen is in continuity with the external environment [5]. Compound/Material absorbed from the lumen must first traverse the epithelium to access mucosal blood, then is carried to liver with portal blood. Except the cells lining the gastrointestinal tract, all other cells of the body are only exposed to flavonoid metabolites and degradation products. Flavonoids probably pass into small intestine as glycosides. Here they can undergo either luminal deglycosylation catalysed by membrane-bound enzymes as lactase-phlorizin hydrolase [11] or enter the enterocytes in form of glycosides requiring active transport [6] followed by intracellular hydrolysis by e.g. broad-specificity cytosolic $\beta$-glucosidase [3]. Flavonoids liberated in the lumen can pass into enterocytes via passive diffusion. Once absorbed, flavonoids are conjugated to glucuronide, sulphate and/or methyl groups mainly in jejunal and ileal enterocytes. The transferases responsible for conjugation are UDP-glucuronyltransferases (UGT; EC 2.4.1.17) and phenolsulfotransferases (PST; EC 2.8.2.1). Methylation is catalysed by catechol O-methyltransferases (COMT; EC 2.1.1.3).

Major products of small intestinal epithelial cell metabolism, quercetin-3- and quercetin-7-glucuronides were shown to be further processed using HepG2 hepatic cell model. One pathway seems to be methylation of catechol moiety of both quercetin glucuronides resulting in 3'-methylquercetin- and 4'-methylquercetin- glucuronides. The other way is deglucuronidation with subsequent sulfation in 3'-position [12].

Colon

Colon is heavily colonised by microorganisms ($\sim10^{12}$/cm$^3$) with enormous catalytic and hydrolytic potential. Flavonoids from food neither absorbed in stomach nor in small intestine and flavonoid metabolites previously absorbed and excreted with bile back to duodenum are propelled to colon. Reaching the colon, they are subject to deglycosylation and deconjugation by colonic bacteria, and are cleaved giving rise to ring fission products, such as phenylacetic, phenylpropionic acids and valerolactones.

Liver

Compounds absorbed from intestines enter the liver via portal vein. Once in the liver, the absorbed substances are removed from the blood by the liver parenchymal cells. The body treats flavonoids as xenobiotics, therefore they are subjected to Phase I (introduction of polar functional groups e.g. -OH) and Phase II (conjugation) biotransformations. Reactions leading to conjugate formation facilitate their clearance and limit their potential toxicity. Recently, a third class of metabolites has also been recognised, namely xenobiotic-macromolecule adducts, also called macromolecular conju-
gates. Due to aromatic nucleus and hydroxyl substituents, flavonoids have a great affinity for proteins, particularly for albumin. Binding of quercetin to human albumin was 70–80% [8]. Another possible way of quercetin intracellular detoxification could be their conjugation with glutathione in 2’-position [15]. Conjugates are eliminated from the liver either with the bile, the gallbladder squirts the bile into duodenum, or renally, i.e., with the blood and urine.

Plasma

Non-conjugated flavonoids are virtually absent from plasma. Day et al. [4] have detected quercetin-3-glucuronide, 3’-methyl-quercetin-3-glucuronide and quercetin-3’-sulphate as major conjugates in human plasma 1.5 hr after onion consumption. A further quercetin conjugate as quercetin-4’-glucuronide [9]. Wittig et al. detected five quercetin glucuronides but no sulfates in plasma 1h after onion consumption using HPLC-UV-MS/MS [16].

Up to now, there has not been reported any accumulation of quercetin in any tissue – as shown in an experiment with radiolabelled quercetin. The highest radioactivity was found in kidney (perhaps due to their concentration by water reabsorption), lower in liver and blood [7]. Similarly, 60 min after orally administered [2-14C]quercetin-4’-glucoside to rats, almost 94% of the recovered radioactivity was still in the pool of stomach, small and large intestines with their contents (denoted as intestine pool) [10]. Also, little is known about the biological activities of low molecular weight ring-fission products.

Conclusion

An attractive hypothesis is that vegetables and fruits contain compounds that have a protective effect for human health, and flavonoids are serious candidates. Within the body, these compounds are extensively metabolised. Therefore, it is important to study the quality, levels, location and biological effects of the arising products.

Literature


**METABOLIZM FLAWONOIDÓW U LUDZI**

**Streszczenie**

Flawonoidy to drugorzędowe metabolity roślin o szerokim zakresie aktywności biologicznej. W ostatnim czasie zainteresowanie nimi znacznie wzrosło, zwłaszcza po tym jak rezultaty badań epidemiologicznych wskazywały, że dieta bogata we flawonoidy może być elementem profilaktyki chorób niedokrwiennej serca i niektórych chorób nowotworowych. Oprócz niektórych spożywczych produktów fermentowanych i herbaty zielonej, większość flawonoidów zawartych w diecie pochodzenia roślinnego to glikozydy, głównie O-glikozydy. Szacuje się, że dziennie spożycie tych związków zawiera się w szerokim zakresie od 150 do 1000 mg.

W artykule skupiono się głównie na metabolizmie kwercetyny, opisując przemiany jakim ulegają flawonoidy w organizmie człowieka. Procesy związane z tymi przemianami to deglikozylacja, przeniesienie do enterocytów, glukuronizacja, transport do wątroby poprzez żyłę wątrobową lub zwrotne wydzielanie do światła jelita oraz dalsze sprzężone reakcje w wątrobie, cyrkulacja wątrobową, wydalanie z żółcią, moczem lub przez jelito grube.

**Słowa kluczowe:** flawonoidy, kwercetyna, wchłanianie, metabolizm, wydzielanie.