The Effects on Metabolism of Glucosinolates and Theirs Hydrolysis Products

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ABSTRACT
Glucosinolates in the nutrition are very important molecules and widely found in Brassicaceae species (brussels sprouts, Dijon mustard, broccoli, cress etc.). Depending on the amount of these kinds of vegetables consumed by humans and animals, some positive or negative metabolic effects of this molecule may occur. Chemically GLS's are the anticarcinogenic molecules that increase the antioxidant effect, the antibiotic activity and induced the phase-II detoxification enzymes. However, there are the studies shown that I3C, a member of the hydrolysis products of GLS's, stimulated and inhibited the carcinogenesis. While the low doses of GLS's may be the antiestrogenic effect, the high doses can an estrogen agonist. Due to the lack of scientific data regarding the dose of the molecule that induces favorable and unfavorable effects on the target tissue, our knowledge of this molecule on induction of potential carcinogenic/anticarcinogenic, estrogen/antiestrogenic, antibiotic effects as well as on regulation of energy balance remains largely insufficient. They constitute the liver, thyroid, rectum abnormalities, and deterioration in the development and reproductive performance. Especially the biological effects, that defines the need to study GLS bioavailability, critically assess the current state of the art on GLS bioavailability, indicate human and animal data on important individual compounds and structural groups, and give recommendations for future research.

Key Words: Brassicaceae; glucosinolate; myrosinase; cancer.

1. INTRODUCTION
The first observations on the unique properties of glucosinolates and isothiocyanates or mustard oils, as they are commonly known, were recorded at the beginning of the 17th century as a result of efforts to understand the chemical origin of the sharp taste of mustard seeds. The discovery and early history of glucosinolates and the participation of the enzyme myrosinase (β-thioglucosidase) in their conversion to isothiocyanates, are the subjects of an interesting and scholarly review by Challenger (1959). The first general, although incorrect, structure for these compounds was proposed at the end of the nineteenth century by Gadamer (1897), who concluded that the side chain was linked to the nitrogen rather than the carbon atom of the “NCS” group. Despite certain difficulties the structure was generally assumed to be correct until 1956, when Ettlinger and Lundeen (1956) pointed out the inadequacies of the Gadamer structure to explain certain properties of these compounds, proposed the now correct structure, and described the first chemical synthesis of a glucosinolate (Ettlinger and Lundeen, 1957).

2. THE CHEMISTRY and HYDROLYSIS of GLUCOSINOLATES
Glucosinolates are abundant plant secondary metabolites that are found in cruciferous plants (e.g. the Brassica spp. vegetables: broccoli, Brussels sprouts, cress and watercress). Naturally occurring GLSs are (Z)-N-hydroximinosulfate esters, possessing a sulfur-linked β-D-glucopyranose moiety and an amino acid-derived side chain (Fig. 1). Side chain and sulfate group have an anti stereochemical configuration across the C=N double bond. More than 120 glucosinolates (β-thioglucoside N-hydroxysulfates) have been isolated and they are biosynthesized from alkyl, thioalkyl (methionine), aromatic, and indole amino acids. Along with their cognate isothiocyanates, glucosinolates such as glucoraphanin (GR) and sulforaphane, have become the subject of intense scrutiny as a result of their cancer chemoprotective, antioxidant, and antibiotic activities and for their potential value as phytochemical components of healthy diets that could be added to functional foods (Fahey et al 2001; Shapiro et al 2001; Talalay and Fahey 2001; Fahey et al; 2002).

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Figure 1 The structure of GLS.

Most GLSs are chemically and thermally stable and therefore hydrolysis is mainly enzymatically driven. Enzymatic hydrolysis involves myrosinase, a β-thioglucosidase that co-occurs in plants with GLSs. Myrosinases have generally been well characterised (Eriksson et al 2001; Hartel and Brandt 2002; Eriksson et al 2002; Bernardi et al 2003). In intact plant tissues, myrosinase is present in compartments separated from its substrate (Bones 1996). Following tissue disruption, enzyme and substrate (GLS) come into contact, causing hydrolysis of the thioglucosidic bond, and thereby yielding glucose and an unstable aglycone, the thiohydroxamate-O-sulfonate (Fig. 2). The latter undergoes spontaneous rearrangement into different possible products: isothiocyanates (ITCs), nitriles and elemental sulfur, thiocyanates, epithionitrites, oxazolidine-2-thiones, or indolyl compounds. The chemical structure of the resulting product depends on the side chain structure and on the reaction conditions (Fig. 2) (Ludikhuyze 2000).

Figure 2 Glucosinolate hydrolysis and the formation of GLS-HPs.

3. JANUS PROPERTIES of GLUCOSINOLATES

Given their promising anticarcinogenic activities, it is not surprising that GLSs and GLS-HPs are being considered and already supplied as the principal components of supplements and “functional foods”. However, most evidence concerning anticarcinogenic effects and the mechanism of action has come from animal studies, and reported carcinogenic and/or toxic effects of GLS-HPs are often ignored. Based on current knowledge, it seems risky to consider giving patients large quantities of ITCs when dose–effect relationships are not clinically proven and the tissue bioavailability is largely unknown. It is certainly possible that some GLS-HPs have properties that are both carcinogenic and chemopreventive. Because of this dual function, they could be referred to as Janus (traditionally depicted as having two faces looking in
opposite directions) carcinogens (Von Borstel and Higgins 1998). Janus carcinogens are defined as carcinogenic compounds that, under differing conditions of cell type or dose, can instead act as anticarcinogens.

4. EFFECTS on CANCER RISK

GLS-HPs, especially ITCs, are amongst the most potent naturally-occurring bioactive compounds intervening in the process of cancer development. The association between Brassica vegetable consumption and cancer risk has been summarised by van Poppel et al (1999), including the results of 6 cohort studies and 74 case-control studies. Data showing that a high Brassica consumption is correlated with a decreased risk of cancer were most consistent for lung, stomach, colon, and rectal, and least consistent for prostate, endometrial, and ovarian cancer. Verhoeven et al (1996) reviewed the results of 7 cohort studies and revealed an inverse correlation between the consumption of individual Brassica vegetables and the risk of lung, stomach, and second primary cancers.

In a recent study, the Karolinska Institute compared the diets of 2832 women aged 50 to 74 years and diagnosed with invasive breast cancer, to the diets of 2650 women of the same age with no history of breast cancer. While there was no correlation between total fruit and vegetable consumption and breast cancer risk, postmenopausal women consuming 1 to 2 servings of Brassica vegetables daily had a 20 to 40% decreased risk of breast cancer (Terry et al 2001).

5. EFFECTS on ESTROGEN STATUS

While at low doses Brassica vegetable extracts may exert antiestrogenic effects, at higher doses they can act as estrogen agonists (Ju et al 2000). Hydrolysis products of indole-GLSs, such as I3C and DIM, are likely to be responsible for the modulation of estrogen receptor activity, with both agonistic and antagonistic properties (Ribri et al 2000; Rahman and Sarkar 2002). Accordingly, I3C increased the 2/16-hydroxyestrone ratio that was found to be predictive of breast cancer risk in some prospective studies. There are preliminary human trials that support a sustained estrogen modifying effect (Brignall 2001), but recent data by Stoner et al (2002) show that, although I3C delayed the latency of mammary tumour formation, it did not alter tumour incidence or multiplicity among survivors. Supporting earlier findings (Nishie and M. E. Daxenbichler 1980; Reddy et al 1983; Babich et al 1993), they also observed a 40% decrease in aberrant crypt foci of the colon by I3C. However, in the liver, I3C strongly induced GST-P foci in carcinogen-treated animals (4-fold increase in volume-% foci) and in vehicle control animals (69-fold increase). It is therefore very likely that I3C both inhibits and, given post-initiation, potentially promotes carcinogenesis. Stoner et al (2002) concluded that because of this potential risk, I3C is not an appropriate chemoprotective agent for human use, in spite of its effects on breast and colon cancer. A long-term clinical use of I3C should be restricted to fully informed, high-risk individuals, for whom the potential therapeutic benefits may be judged to outweigh its risk potential. The fact that there are supplements available that claim to contain I3C and DIM with increased bioavailability should raise concerns and the demand for regulatory action.

6. CONCLUSION

Especially the biological effects, that defines the need to study GLS bioavailability, critically assess the current state of the art on GLS bioavailability, indicate human and animal data on important individual compounds and structural groups, and give recommendations for future research. However, little information is available on the metabolisms of hydrolysis products derived from the glucosinolates, because it could be found any work revealed of the beneficial and harmful effects of the GLS and the hydrolysis products in the literature researches regarding the dose adjustment.

Depending on the amount of these kinds of vegetables consumed by humans and animals, some positive or negative metabolic effects of this molecule may occur. Chemically GLS’s are the anticarcinogenic molecules that increase the antioxidant effect, the antibiotic activity and induced the phase-II detoxification enzymes. However, there are the studies shown that I3C, a member of the hydrolysis products of GLS’s, stimulated and inhibited the carsinogenesis. While the low doses of GLS's may be the antiestrogenic effect, the high doses can an estrogen agonist. Due to the lack of scientific data regarding the dose of the molecule that induces favorable and unfavorable effects on the target tissue, our knowledge of this molecule on induction of potential carcinogenic/anticarcinogenic, estrogenic/antiestrogenic, antibiotic effects as well as on regulation of energy balance remains largely insufficient. They constitute the liver, thyroid, rectum
abnormalities, and deterioration in the development and reproductive performance. According to latest information, it needs to be done of the new studies which will clarify these issues due to unknown of the dose that form the beneficial and harmful effects of molecules in the target tissue. In recent years, energy homeostasis, adiponecin, ghrelin and leptin with the discovery of hormones has become widespread a research center. They are an important indicator about current status of the energy balance because of their roles in regulating of the energy expenditure and nutrient intake. It is necessary to compare with different body compositions and to determine the parameters in respect to nutrient intake and appetite with these hormones to see the effects of GLS’s.

REFERENCES


