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Bioavailability and *in vivo* metabolism of intact glucosinolates

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ABSTRACT

Health benefits associated with consumption of cruciferous vegetables have received considerable attention with a hitherto focus on the role and bioactivity of glucosinolate degradation products. We investigated the *in vivo* metabolism of intact glucosinolates by following their fate in digesta and in the endogenous metabolism in pigs. This is the first study to show an intact glucosinolate, sinalbin, being absorbed and transformed to a sinalbin metabolite in the liver by glucuronidation expectedly performed by liver phase II enzymes with subsequent excretion to the urine. From LC–MS/MS data we propose a structure of the sinalbin metabolite as containing two 4-oxybenzyl groups. Sinalbin and the metabolite were detected in plasma from the hepatic vein with a ratio of metabolite to sinalbin of approximately 12:1 after 2–4 hours. Induction of liver phase II enzymes by intact glucosinolates indicates that these also themselves are bioactive compounds with potential health risks or beneficial effects.

1. Introduction

Intact glucosinolates and their transformation products are bioactive compounds responsible for smell, taste and metabolic effects when they are present in food or feed consumed by monogastrics. In particular, glucosinolate degradation products have been investigated for their possible physiological effects with a specific food perspective on the effects of the degradation products as reviewed by Holst and Williamson (2004) and Jeffery and Araya (2009). Glucosinolates are as intact compounds present in all plants of the order Capparales and only in few other plants (Bellostas, Sørensen, Sørensen, & Sørensen, 2007; Bones & Rossiter, 2006; Fahey, Zalcmann, & Talalay, 2001). Glucosinolates comprise a group of more than 140 structurally different compounds with well-defined structure, chemotaxonomic occurrence and co-occurring in the plant with myrosinase isoenzymes (EC 3.2.1.147). However, only few types of glucosinolates are generally present in individual plant species and plant parts. The well-defined structures of glucosinolates consist of alkyl-N-hydroximine-O-sulphate esters with a β-D-thioglucopyranoside group attached to the hydroximine carbon in Z-configuration to the sulphate group (Bellostas et al., 2007; Bones & Rossiter, 2006; Ettlinger & Kjaer, 1968; Ettlinger & Lundeen, 1956, 1957; Fahey et al., 2001; Kjaer, Thomsen, & Hansen, 1960; Sørensen, 1990) (Fig. 1).

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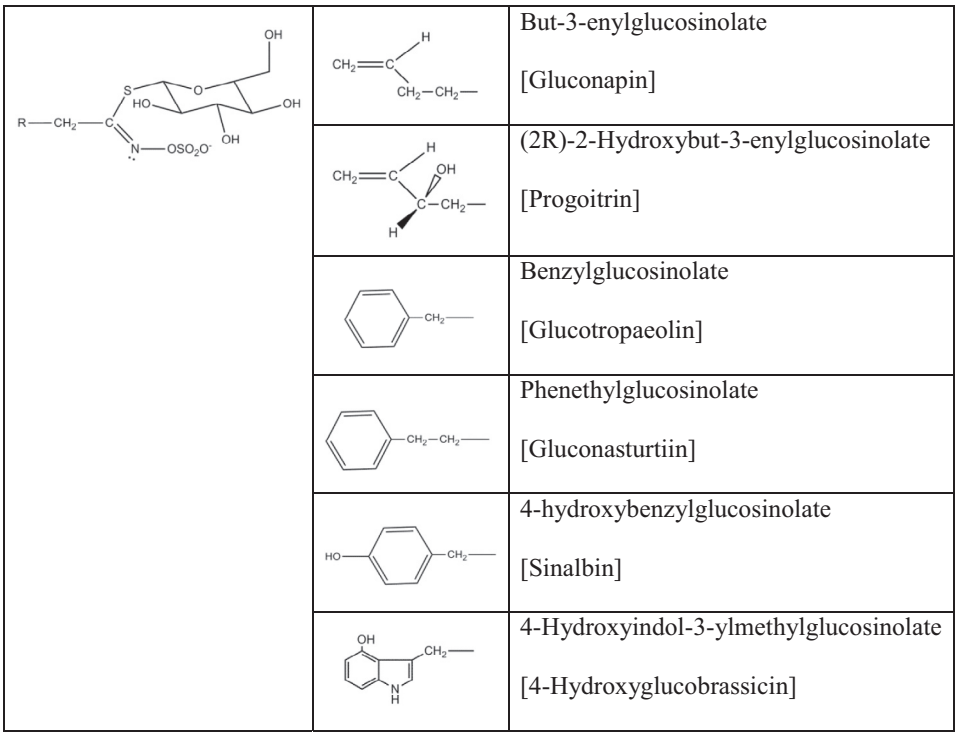

Fig. 1 – Structure and names of selected glucosinolates included in pig diets: semisystematic- and [trivial] names.

In the genus *Sinapis*, sinalbin (4-hydroxybenzylglucosinolate) is the dominating glucosinolate (Buskov et al., 2000a; Griffiths, Birch, & Hillman, 1998), whereas quantitatively dominating glucosinolates in double low rapeseed are progoitrin, gluconapin and 4-hydroxyglucobrassicin (Bellostas et al., 2007; Fahey et al., 2001). The interest in sinalbin and other food and feed relevant glucosinolates is closely linked to the physico-chemical-biochemical properties of both intact glucosinolates and especially the complex group of glucosinolate degradation products produced in autolysis-, non-enzymatic- and myrosinase-catalysed reactions. The composition of the degradation products is to a great extent defined by reaction conditions and by the glucosinolate structures (Agerbirk, Olsen, & Sørensen, 1998; Bellostas, Petersen, Sørensen, & Sørensen, 2008a; Bellostas et al., 2007; Bellostas, Sørensen, Sørensen, & Sørensen, 2008b, 2009; Bones & Rossiter, 2006; Buskov et al., 2000a; Buskov, Olsen, Sørensen, & Sørensen, 2000b; Griffiths et al., 1998). Sinalbin has electrophilic properties at the methylene carbon in the benzyl group corresponding to that of the indol-3-ylmethyl carbon in indol-3-ylmethylglucosinolates, resulting in easy release of the thiocyanate ion and the 4-hydroxybenzylgroup from the thiohydroxamate or 4-hydroxybenzylisothiocyanate (Agerbirk et al., 1998; Buskov et al., 2000a,b).

The bioactivity and specific biological effects resulting from use of glucosinolate containing plant materials in feed and food depend on the actual structures and concentrations both of the intact glucosinolates and the various transformation products reaching the digestive system, internal organs and the xenobiotic systems and metabolism (Andersen et al., 2010; Bille, Eggum, Jacobsen, Olsen, & Sørensen, 1983; Bjerg, Eggum, Jacobsen, Otte, & Sørensen, 1989; Jeffery & Araya, 2009; Kloss et al., 1996; Lai, Miller, & Jeffery, 2010; Song, Morrison, Botting, & Thornalley, 2005). So far a great deal of attention has been devoted to the bioavailability of isothiocyanates, and especially to the isothiocyanate sulphoraphane (Holst & Williamson, 2004; Jeffery & Araya, 2009), with a particular focus on the link between reduction of cancer risk and consumption of broccoli (Jeffery & Araya, 2009). Several studies have confirmed that sulphoraphane is absorbed or transported across the intestinal wall, since sulphoraphane metabolites have been detected in the urine and plasma (Bheemreddy & Jeffery, 2007; Clarke et al., 2011; Song et al., 2005; Vermeulen, Klopping-Ketelaars, van den Berg, & Vaes, 2008; Vermeulen, van den Berg, Freidig, van Bladeren, & Vaes, 2006).

Previous investigations have thus mainly focused on biologic effects from the glucosinolate transformation products, whereas possible effects from the intact glucosinolates in the diet/digesta rarely have been studied. Previous experiments with rats have shown that intake of too high levels of intact glucosinolates has negative effects on protein utilization and on internal organs (Andersen et al., 2010). Several intact glucosinolates were tested in these studies, and the intact glucosinolates as well as myrosinase catalysed reaction products gave rise to significant biologic effects in the animals (Andersen et al., 2010; Bille et al., 1983; Bjerg et al., 1989). The effects varied as a response to the glucosinolate structure and concentration (Andersen et al., 2010), and only in some cases the presence of myrosinase led to increased biological effects. For sinalbin, increasing the dietary levels reduced the biological value of dietary protein, whereas inclusion of myrosinase in the diet did not further reduce the biological value (Bille et al., 1983).

We need, therefore, more specific knowledge on the actual structure and concentration of the compounds causing the