Absorption and metabolism of caffeic acid and chlorogenic acid in the small intestine of rats

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The absorption and metabolism in the small intestine of chlorogenic acid (5-O-caffeoylquinic acid), the main phenolic acid in the human diet, and of caffeic acid were studied in rats in order to determine whether chlorogenic acid is directly absorbed or hydrolysed in the small intestine. Chlorogenic and caffeic acids were perfused into a segment of ileum plus jejunum during 45 min (50 of caffeic acid were studied in rats in order to determine whether chlorogenic acid is directly absorbed or hydrolysed in the small intestine. Chlorogenic and caffeic acids were perfused into a segment of ileum plus jejunum during 45 min (50 μM, 0.75 ml/min) using an in situ intestinal perfusion rat model with cannulation of the biliary duct, and were quantified together with their metabolites in perfusion effluent, bile and plasma. The net absorption (influent flux minus effluent flux of phenolic acids and their metabolites) accounted for 19.5 % and 8 % of the perfused caffeic and chlorogenic acids, respectively. A minor fraction of the perfused caffeic acid was metabolized in the intestinal wall and secreted back into the gut lumen in the form of ferulic acid (0.5 % of the perfused flux). Part of the chlorogenic acid (1.2 % of the perfused flux) was recovered in the gut effluent as caffeic acid, showing the presence of trace esterase activity in the gut mucosa. No chlorogenic acid was detected in either plasma or bile, and only low amounts of phenolic acids (less than 0.4 %) were secreted in the bile. The present results show that chlorogenic acid is absorbed and hydrolysed in the small intestine. In contrast to numerous flavonoids, absorbed phenolic acids are poorly excreted in the bile or gut lumen. Their bioavailability therefore appears to be governed largely by their uptake into the gut mucosa.

Caffeic acid: Chlorogenic acid: Intestinal perfusion: Absorption: Rat

Hydroxycinnamamic acids are one of the major classes of phenolic compounds. They are present in a large variety of fruits and vegetables (Clifford, 1999; Manach et al. 2004). The major representative of hydroxycinnamic acids in food is caffeic acid. It occurs largely conjugated with quinic acid, as in chlorogenic acid (5-O-caffeoylquinic acid; Fig. 1). Coffee, one of the most widely consumed beverages in the world, is the major dietary source of chlorogenic acid. Regular coffee-drinkers commonly ingest 0.5–1 g chlorogenic acid/d, corresponding to about 250–500 mg caffeic acid/d (Clifford, 1999).

Caffeic acid and chlorogenic acid have antioxidant properties, illustrated by their ability to scavenge various free radicals when tested in vitro (Ohnishi et al. 1994; Nardini et al. 1995; Abu-Amsha Caccetta et al. 1996; Rice-Evans et al. 1996; Foley et al. 1999; Laranjinha & Cadenas, 1999). In vivo, when ingested with the diet, caffeic acid and chlorogenic acid increase the plasma antioxidant capacity, the concentrations of endogenous antioxidants such as vitamin E and the ex vivo resistance of lipoproteins to oxidation (Nardini et al. 1997; Natella et al. 2002; Lafay et al. 2005). Chlorogenic acid is also able to reverse the pro-oxidant effects of drugs such as paraquat (Tsuehiya et al. 1996). Chlorogenic acid and caffeic acid have been reported to prevent different cancers and CVD in several experimental studies on animal models (Mori et al. 1986; Tanaka et al. 1990, 1993; Zhou et al. 1993; Suzuki et al. 2002).

The biological properties of hydroxycinnamic acids depend on their absorption in the gut and on their metabolism. The absorption of caffeic acid in the small intestine has been well characterized in both experimental animals and in man (Teuchy & Van Sumere, 1971; Camarasa et al. 1988; Azuma et al. 2000; Othof et al. 2001; Simonetti et al. 2001; Scalbert et al. 2002), but the bioavailability of chlorogenic acid is more controversial.

In some studies, chlorogenic acid has been detected in urine with a recovery varying from 0.3 % to 2.3 %, suggesting absorption without structural modification (Cremin et al. 2001; Othof et al. 2001; De Maria & Moreira, 2004; Ito et al. 2005). Other authors have failed to detect chlorogenic acid in the plasma of both rats and man after its ingestion as a pure compound or in coffee (Choudhury et al. 1999; Azuma et al. 2000; Nardini et al. 2002). Caffeic acid and its O-methylated metabolites are commonly found in plasma and urine after ingestion of chlorogenic acid in rats and man, showing that chlorogenic acid is hydrolysed in the body (Azuma et al. 2000; Rechner et al. 2001a; Nardini et al. 2002; Wittmer et al. 2005).

Such a reaction could either take place in the gut mucosa or arise from catalysis by the gut microflora. No esterase
activity able to hydrolyse chlorogenic acid could be detected in human tissues (intestinal mucosa, liver) or biological fluids (plasma, gastric juice, duodenal fluid) in rats or man (Plumb et al. 1999; Azuma et al. 2000; Andreasen et al. 2001; Olthof et al. 2001; Rechner et al. 2001b). On the other hand, microflora in the large intestine possess esterase activity towards chlorogenic acid (Couteau et al. 2001; Rechner et al. 2004). These results suggest that caffeic acid found in plasma originates from the hydrolysis of chlorogenic acid in the colon. This would, however, be inconsistent with the rapid detection (30 min after administration of chlorogenic acid) of caffeic and ferulic acids in the plasma of rats (Azuma et al. 2000).

The aim of the present work was therefore to examine whether chlorogenic acid is absorbed or hydrolysed in the small intestine. The absorption and metabolism of chlorogenic acid in the small intestine were explored using an in situ intestinal perfusion model (segment of ileum plus jejunum) and compared with those of caffeic acid. Such a model has been used in different laboratories to study the intestinal absorption and metabolism of polyphenols (Crespy et al. 1999; Andlauer et al. 2000; Sesink et al. 2003; Arts et al. 2004; Talavera et al. 2004). Chlorogenic and caffeic acids were analysed together with their main metabolites in the perfusion effluent, bile and plasma.

Materials and methods

Chemicals

β-Glucuronidase/sulfatase from Helix pomatia (type H2) and from Escherichia coli (type X-A), chlorogenic acid, caffeic acid and ferulic acid were purchased from Sigma (L’Isle d’Abeau Chesnes, France). Isoferulic acid was purchased from Extrasynthèse (Genay, France).

Animals and diets

Eight Wistar rats, born at the Institut National de la Recherche Agronomique and weighing approximately 150 g, were housed, two per cage, in temperature-controlled rooms (22°C), with a dark period from 20.00 hours to 08.00 hours and with access to food from 16.00 hours to 08.00 hours. They were fed a standard semi-purified diet (composition, per kg of diet: 755 g wheat starch, 150 g casein, 50 g peanut oil, 35 g mineral AIN-93M mixture, 10 g vitamin AIN-93 mixture supplemented with 1.36 g choline) for 2 weeks. Animals were maintained and handled according to the recommendations of the National Institute for Agricultural Research Ethics Committee, in accordance with Decree 87-848.

In situ gut perfusion

Rats were anaesthetized with sodium pentobarbital (40 mg/kg body weight) 24 h after the end of the last meal by intraperitoneal injection, maintained at 37°C on a heat plate and kept alive during the perfusion period. After cannulation of the biliary duct, a perfusion of a jejunal and ileal segment of intestine (from the duodeno-jejunal flexure to 5 cm distal to the ileocaecal valve) was prepared by installing cannulas at each extremity.

This segment was continuously perfused in situ with a buffer containing KH2PO4 (5 mmol/l), K2HPO4 (2.5 mmol/l), NaHCO3 (5 mmol/l), NaCl (50 mmol/l), KCl (50 mmol/l), CaCl2 (2 mmol/l), MgCl2 (2 mmol/l), glucose (10 mmol/l) and taurocholic acid (1 mmol/l; pH adjusted at 6.7) and supplemented with 50 μM-caffeic acid (n 4) or 50 μM-chlorogenic acid (n 4). A flow rate of about 0.75 ml/min and a temperature of 37°C were maintained during the 45 min of the perfusion (Crespy et al. 1999; Andlauer et al. 2000; Sesink et al. 2003; Arts et al. 2004; Talavera et al. 2004). The average flow rate was determined for each experiment over the 45 min of perfusion. These quantities of chlorogenic acid perfused correspond to an intake in man of about 500 mg chlorogenic acid (calculated for rats and human subjects consuming, respectively, 20 g and 500 g DM/d). This amount of chlorogenic acid corresponds to three or four cups of coffee (Scalbert & Williamson, 2000).

Both caffeic and chlorogenic acids were quantified in the buffer at the end of the experiment and found to be stable in the buffer throughout the perfusion period. The effluent at the exit of ileum and the bile were collected throughout the 45 min of the perfusion period for analysis of phenolic acids. At the end of the experiment, blood samples were withdrawn from the mesenteric vein into heparinized tubes. Perfusate, bile and plasma samples were acidified with 10 mM-acetic acid and stored at –20°C.

Fig. 1. Chemical structure of caffeic acid, chlorogenic acid, ferulic acid and isoferulic acid.
Analysis of phenolic acids

Sample treatment. Perfusate, bile and plasma samples were spiked at 5 μmol/l with sinapic acid or vanillic acid as internal standard. Samples collected after caffeic acid perfusion were acidified to pH 4.9 with 0.1 volume of 0.5 M-sodium acetate containing 2 g ascorbic acid/l (pH 3). Perfusate and bile samples were incubated for 45 min at 37°C, and plasma samples for 4 h at the same temperature, in the presence of 10⁸ units β-glucuronidase and 2.5 × 10⁶ units sulfatase from H. pomatia per litre.

The procedure was modified for samples collected after chlorogenic acid perfusion as we noticed that chlorogenic acid was partially hydrolysed by H. pomatia enzymes (Ito et al. 2005). Samples were then adjusted to pH 6.8 with 0.1 volume of 0.5 M-sodium acetate containing 2 g ascorbic acid/l (pH 4.9). Perfusate and bile samples were incubated for 45 min at 37°C, plasma samples for 4 h at the same temperature, in absence or in the presence of 2 × 10⁶ units β-glucuronidase from E. coli per litre. No caffeic acid was formed in these conditions, as confirmed by the addition of pure chlorogenic acid to a control plasma containing the enzyme from E. coli. Sulfatase activity was also present in the enzyme fraction as observed using a rat plasma sample containing known sulfate esters of quercetin (data not shown).

Samples were extracted by adding 2.85 volumes of methanol–H₂O–concentrated HCl (70:28:2, by vol.) and centrifuged for 4 min at 12 000 g. The resulting supernatant was analysed as described below.

Determination of the intestinal and biliary fluxes. All the calculated fluxes were expressed in nmol/min. The fluxes in the effluent were calculated taking into account the intestinal absorption of H₂O as previously described (Crespy et al. 1999). For a given phenolic acid, the net transfer into the enterocyte was evaluated by the difference between the perfused flux and the flux of perfused molecules recovered in the non-hydrolysed effluent at the end of the perfusion. The secretion of conjugates back into the gut lumen was determined as the difference between the flux of perfused molecules measured in the non-hydrolysed effluent and the flux of total phenolic acids in the hydrolysed effluent. The net absorption was calculated as the difference between the net transfer into the enterocyte and the intestinal secretion of metabolites (O-methylated conjugated forms). The biliary secretion of conjugated forms was determined as the product between the biliary flow rate (μl/min) and the concentrations of the phenolic acids measured in the bile after enzymatic hydrolysis (μmol/l).

Chromatographic conditions. The conjugated metabolites of phenolic acids were analysed by HPLC coupled to an eight-electrode CoulArray Model 5600 detector (Eurosep, Cergy, France) with potentials set at 25, 100, 250, 325, 400, 475 and 550 mV. The system was fitted with a 5 μm C-18 Hypersil BDS analytical column (150 × 4.6 mm; Life Sciences International, Cergy, France). Mobile phase A was 5% acetonitrile in 30 mM-NaH₂PO₄ at pH 3, and mobile phase B was 50% acetonitrile in 30 mM-NaH₂PO₄ at pH 3. The separation was performed at 35°C. The flow rate was 0.8 ml/min, and the following gradient was applied: linear gradient from 0% to 22% B from 0 to 21 min; linear gradient from 22% to 29% B from 21 to 41 min; 100% B from 41 to 45 min. The identification of phenolic acids was based on the comparison with appropriate commercial standards (Fig. 2). In perfused buffer, detection limits were 0.06 μmol/l for chlorogenic, caffeic and isoferulic acids, and 0.08 μmol/l for ferulic acid. In bile and plasma, detection limits were 0.06 μmol/l for caffeic and isoferulic acids, and 0.08 μmol/l for ferulic acid.

Data analysis

Data were treated with the Instat statistical program (Instat, San Diego, CA). Values are given as means with their standard errors. An unpaired t test or Mann–Whitney test (non-parametric test) was applied to determine differences.

Fig. 2. Chromatogram of a control plasma spiked with chlorogenic, vanillic, caffeic, ferulic, sinapic and isoferulic acid standards. See text (this page) for details of method.
between values. Differences with a value of $P<0.05$ were considered significant.

**Results**

**Intestinal metabolism of caffeic acid**

When caffeic acid was perfused at 44.6 (SE 1.3) nmol/min into the upper intestinal tract, both caffeic and ferulic acids were recovered in the effluent at the end of perfusion. Their respective fluxes in the non-hydrolysed effluent were 35.7 (SE 1.1) and 0.17 (SE 0.01) nmol/min (Table 1). These two fluxes correspond to respectively 80% and 0.4% of the perfused flux of caffeic acid (Fig. 3). The net transfer of caffeic acid into the enterocyte was 8.8 (SE 0.7) nmol/min, corresponding to 20% of the perfused flux.

When the effluent was treated by a β-glucuronidase/sulfatase, the flux of caffeic acid did not change significantly – 36.7 (SE 1.2) vs. 35.7 (SE 1.1) nmol/min in non-hydrolysed effluent – indicating the absence of intestinal secretion of conjugates for caffeic acid. Conversely, the flux of ferulic acid in the effluent significantly increased after enzymatic hydrolysis (0.17 (SE 0.01) vs. 0.23 (SE 0.01) nmol/min in non-hydrolysed and hydrolysed effluent; $P<0.05$), showing a release of ferulic acid conjugates. As the biliary duct had been cannulated before starting perfusion, the ferulic acid and conjugated derivatives found in the effluent at the end of perfusion had an intestinal origin and represented 0.5% of the perfused flux. Thus, the recovery of caffeic acid and its metabolites accounted for 80.5% of the perfused flux. The net absorption of caffeic acid is therefore determined by the difference between the perfused flux of caffeic acid and the flux of total phenolic acids in the effluent, accounting for 19.5% of the perfused flux.

<table>
<thead>
<tr>
<th>Mean</th>
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<td>Caffeic acid</td>
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<td>1.3</td>
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<td>Chlorogenic acid</td>
<td>–</td>
<td>–</td>
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<td>Non-hydrolysed effluent (free phenolic acids)</td>
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<tr>
<td>Chlorogenic acid</td>
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<tr>
<td>Caffeic acid</td>
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<td>Ferulic acid</td>
<td>0.17</td>
<td>0.01</td>
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<td>Isoferulic acid</td>
<td>ND</td>
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<tr>
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<td>–</td>
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<tr>
<td>Net absorption ‡</td>
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<td>0.4</td>
<td>3.2</td>
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ND, not detected.

* $P<0.05$ v. non-hydrolysed effluent flux.

† Net transfer = perfused flux – non-hydrolysed effluent flux of caffeic or chlorogenic acid.

‡ Net absorption = net transfer – intestinal secretion of metabolites.

**Intestinal metabolism of chlorogenic acid**

When chlorogenic acid was perfused at 40.4 (SE 0.8) nmol/min into the upper intestinal tract, both chlorogenic and caffeic acids were recovered in the effluent at the end of perfusion. Their respective fluxes in the non-hydrolysed effluent were 36.7 (SE 1.1) nmol/min and 0.23 (SE 0.01) nmol/min (Table 1). These phenolic acids fluxes correspond to 90.8% and 0.6% of the perfused flux of chlorogenic acid respectively (Fig. 3). The net transfer of chlorogenic acid into the enterocyte was 3.7 (SE 0.7) nmol/min, corresponding to 9.2% of the perfused flux.

When the effluent was treated with deconjugating enzymes, the flux of chlorogenic acid was not changed – 36.7 (SE 0.3) vs. 36.7 (SE 1.1) nmol/min in non-hydrolysed effluent – indicating the absence of intestinal secretion of conjugates of chlorogenic acid. After enzymatic hydrolysis, the flux of caffeic acid significantly increased (0.48 (SE 0.02) nmol/min; $P<0.05$ v. caffeic acid in non-hydrolysed effluent), indicating the presence of caffeic acid conjugates released in the lumen. Free caffeic acid and conjugated derivatives found in the effluent resulted from intestinal activity, and their secretion into the lumen represented 1.2% of perfused flux. Thus, net absorption of chlorogenic acid was 3.2 (SE 0.8) nmol/min and accounted for 8% of the perfused flux.

**Metabolites excreted in the bile after perfusion of hydroxycinnamic acids**

Phenolic acids were analysed in the bile after enzymatic deconjugation. Three phenolic acids – caffeic, ferulic and isoferulic acid – were found in the bile after caffeic acid perfusion (Table 2). The respective biliary fluxes were 109 (SE 23) pmol/min, 35.0 (SE 5.0) pmol/min and 26.3 (SE 1.5) pmol/min. Caffeic acid was also found in low concentration in the bile after chlorogenic acid perfusion (Table 2).

**Metabolites recovered in the plasma after perfusion of hydroxycinnamic acids**

Phenolic acids were analysed after enzymatic deconjugation in the plasma mesenteric vein. Samples collected after the perfusion of caffeic acid showed the presence of ferulic and isoferulic acids (Table 3). Low amounts of caffeic acid were also detected in the mesenteric vein of two rats. Analysis of the plasma samples collected after chlorogenic acid perfusion showed the presence of isoferulic acid in mesenteric plasma.

**Discussion**

Epidemiological and clinical studies have shown that the consumption of coffee, a major dietary source of chlorogenic acids, reduces the risk of non-insulin-dependent diabetes, decreases hyperglycaemia and increases plasma antioxidative capacity (Natella et al. 2002; van Dam & Feskens, 2002; Yamaji et al. 2004). Coffee polyphenols, particularly chlorogenic acid, could contribute to these effects (Scalbert et al. 2005). The biological effects of polyphenols rely largely on their bioavailability (Manach et al. 2004), but the bioavailability...
Intestinal metabolism of phenolic acids have been poorly studied. The in situ perfusion of caffeic and chlorogenic acids into a segment of the upper intestinal tract of rats (jejunum plus ileum) allows us to compare their absorption in conditions close to normal physiology.

The esterification of caffeic acid, as with chlorogenic acid, more than halved its absorption: 19.5% and 8% of the perfused flux for caffeic and chlorogenic acids, respectively, were absorbed. Using the same model of perfusion as used here, the intestinal absorption of ferulic acid has been determined and was higher than that of caffeic acid (56.1% v. 19.5% of the perfused flux respectively; Adam et al. 2002), showing that the O-methylation of caffeic acid increases its transfer through the intestinal barrier. Similar conclusions were obtained by perfusing an isolated rat intestinal segment (Spencer et al. 1999). The values for net transfer of caffeic and chlorogenic acids through the small intestine also appear much lower than those observed for flavonoids, using the same in situ perfusion model, which varied from 35.2% for catechin to 78% for kaempferol (Crespy et al. 2003).

The absorption of different phenolic acids has also been studied with Caco-2 cell monolayers (Konishi et al. 2003a,b; Konishi & Kobayashi, 2004). The transepithelial flux of chlorogenic acid was found to be much lower than that of caffeic acid, which was itself lower than that of ferulic acid, in agreement with the present results. Free phenolic acids would largely be absorbed through an active mechanism involving monocarboxylic acid transporters, whereas the absorption of chlorogenic acid would follow the paracellular route. In experiments with volunteers who had undergone colonic ablation, chlorogenic acid absorption was also three times lower than that of caffeic acid, a proportion comparable to the one observed in the present work (Olthof et al. 2001).

Chlorogenic acid has been identified by several authors in urine after the ingestion of coffee or pure chlorogenic acid, suggesting a direct absorption in the gut (Cremin et al. 2003).

| Table 2. Biliary flux of phenolic acids after in situ perfusion of caffeic acid or chlorogenic acid* |
|---------------------------------|---------------------------------|
| Caffeic acid perfusion (pmol/min) | Chlorogenic acid perfusion (pmol/min) |
| Mean  | SE   | Mean  | SE   |
| Caffeic acid | 109  | 23    | 3-0  | 1-3 |
| Ferulic acid | 35-0 | 5-0   | ND   |     |
| Isoferulic acid | 28-3 | 1-5   | ND   |     |

ND, not detected.

* Biliary flux = concentration of (free + conjugated) phenolic acid x biliary flow. Biliary flow was 15.1 (st 2.3) ml/min for caffeic acid and 15.6 (st 2.6) ml/min for chlorogenic acid.

| Table 3. Concentrations of caffeic acid metabolites and chlorogenic acid metabolites in the mesenteric plasma of rats after perfusion with caffeic acid or chlorogenic acid |
|---------------------------------|---------------------------------|
| Caffeic acid (µM) | Chlorogenic acid (µM) |
| Mean  | SE   | Mean  | SE   |
| Caffeic acid | Trace | ND     |
| Ferulic acid | 0.71 | 0.04  | ND   |
| Isoferulic acid | 0.14 | 0.01 | 0.12 | 0.02 |
| Chlorogenic acid | ND | ND       |

ND, not detected (limits of detection for caffeic, chlorogenic and isoferulic acids 0.06 µM and for ferulic acid 0.08 µM).
isoferulic acid, a reaction catalysed by catechol-O-methyltransferase previously identified in the intestine (Mańnisto et al. 1999). Some of this ferulic acid was secreted back to the intestinal lumen during caffeic acid perfusion. Ferulic & Kaakkola, 1999). Some of this ferulic acid was secreted back into the gut lumen during caffeic acid perfusion. Ferulic and isoferulic acids identified in the bile could originate from ferulic acid conjugates determined in the effluent after the perfusion of chlorogenic acid represented 0·6 % of the perfused flux. Similar experiments, carried out with different flavonoids, have shown wide variations in the levels of conjugates secreted back to the gut lumen, from 0 % of the perfused flux for catechin to 52 % for quercetin (Crespy et al. 2003). The present results show that the secretion of hydroxycinnamic acid conjugates into the gut lumen is low compared with that of some flavonoids, in agreement with a previous study on ferulic acid (Adam et al. 2002).

The biliary excretion of hydroxycinnamic acids has previously been established by liver perfusion or intraperitoneal injection of caffeic acid in the rat (Scheline, 1968; Gumbinger et al. 1993). In the present work, biliary excretion did not exceed 0·4 % of the perfused dose of caffeic acid, suggesting a limited contribution of this route.

The splanchnic metabolism of caffeic and chlorogenic acids is summarised in Fig. 3. A total of 19·5 % of the caffeic acid and 8 % of the chlorogenic acid perfused through the small intestine reached the mesenteric blood. A minute fraction of the phenolic acids transferred into the gut mucosa was secreted back to the intestinal lumen as ferulic acid for caffeic acid perfusion and caffeic acid for chlorogenic acid perfusion. This result demonstrates for the first time the in vivo hydrolysis of chlorogenic acid in the gut mucosa, but esterase activity towards this phenolic acid appears very low. Phenolic acids found in the mesenteric blood reached the liver, where a low fraction was excreted into the bile in its unchanged or O-methylated form, showing that biliary excretion is not the major route of excretion for phenolic acids. Therefore, the fraction of phenolic acids reaching the peripheral tissues (19·1 % and 8 % for caffeic and chlorogenic acid, respectively) depends largely on the absorption through the gut barrier.

The present results for caffeic and chlorogenic acids can be compared with those previously obtained with other polyphenols using the same in situ perfusion model (Crespy et al. 2003). For example, the fractions of eryodictiol and quercetin reaching the peripheral tissues were similar (20 % and 9 %, respectively) to that observed here for phenolic acids. However, their splanchnic metabolism differs significantly from that of caffeic and chlorogenic acids. Quercetin is characterized by high intestinal uptake (67 %), high secretion back into the gut lumen (52 %) and significant secretion into the bile (6 %). Eryodictiol also showed a high intestinal uptake (59 %), a moderate secretion back into the gut lumen and a high biliary excretion (23 %). Caffeic and chlorogenic acids also differ from ferulic acid, which showed a significant excretion through the bile (6 %; Adam et al. 2002). Therefore, the factors determining the bioavailability of polyphenols in inner body tissues vary according to polyphenols. The bioavailability of caffeic and chlorogenic acids appears to be largely determined by their uptake into the gut mucosa, as previously reported for catechin (Crespy et al. 2003).

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References


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