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Resveratrol has been widely investigated for its potential health properties, although little is known about its metabolism *in vivo*. Here we investigated the distribution of metabolic products of [3H]*trans*-resveratrol, following gastric administration. At 2 h, plasma concentrations reached 1·7 % of the administered dose, whilst liver and kidney concentrations achieved 1·0 and 0·6 %, respectively. Concentrations detected at 18 h were lower, being only 0·5 % in plasma and a total of 0·35 % in tissues. Furthermore, whilst kidney and liver concentrations fell to 10 and 25 %, respectively, of concentrations at 2 h, the brain retained 43 % of that measured at 2 h. Resveratrol-glucuronide was identified as the major metabolite, reaching 7 μM in plasma at 2 h. However, at 18 h the main form identified in liver, heart, lung and brain was native resveratrol aglycone, indicating that it is the main form retained in the tissues. No phenolic degradation products were detected in urine or tissues, indicating that, unlike flavonoids, resveratrol does not appear to serve as a substrate for colonic microflora. The present study provides additional information about the nature of resveratrol metabolites and which forms might be responsible for its *in vivo* biological effects.

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene), a natural polyphenol identified as a biologically active compound in red wine (Siemann & Creasy, 1992), has been the focus of various *in vivo* and *in vitro* studies aimed at investigating its effect on multiple pathophysiological processes and conditions. It has been reported to possess anti-inflammatory (Kimura *et al.* 1985), vasorelaxing (Jager & Nguyen-Duong, 1999) and anti-tumour (Jang *et al.* 1997; Lu & Serrero, 1999) properties, and it has been demonstrated to inhibit platelet aggregation (Kimura *et al.* 1985) and lipid peroxidation (Fauconneau *et al.* 1997) *ex vivo*. These bioactivities of resveratrol have been proposed to be causally linked to the lower prevalence of CHD that is epidemiologically associated with a moderate consumption of red wine (Soleas *et al.* 1997).

Despite the number of studies published on the biological activity of resveratrol, our knowledge regarding absorption, metabolism and, especially, tissue distribution of resveratrol is limited. However, it has previously been established that O-glucuronidation, occurring either in the small intestine (Spencer *et al.* 1999) or in the liver (Scheline, 1991), represents a major metabolic pathway for various phenolic phytochemicals, including resveratrol and the more complex flavonoids. In this context, Soleas *et al.* (2001) have demonstrated that following intra-gastric administration of [H3]*trans*-resveratrol, the overall levels of radiolabelled compounds in serum declined far more slowly than those of the

radiolablled test compound, suggesting the presence of metabolism-derived resveratrol derivatives. Indeed, resveratrol-3-*O*-glucuronide was later identified as the most abundant metabolite of resveratrol in the rat (Marier *et al.* 2002; Yu *et al.* 2002) and in human plasma (Goldberg *et al.* 2003; Wang *et al.* 2004) following the ingestion of chemically pure resveratrol. In addition, previous studies (Vitrac *et al.* 2003) have also demonstrated the presence of glucuronidated resveratrol derivatives in certain tissues of rat. However, little is known about the dynamics of resveratrol metabolism, and effects of time on the tissue distribution and the excretion of resveratrol and its main structurally related metabolites.

Other plant-derived phenolic compounds, including various flavonoids, have also been shown to undergo biotransformation by the colonic microflora (Rechner *et al.* 2002), thus yielding small, structurally distinct cleavage products that are often hydroxylated derivatives of simple phenolic acids or γ-valerolactones. In this context it is interesting to note that the resveratrol products that arise from colonic fermentation processes are yet to be identified.

The present study was aimed at investigating the time-dependent appearance and disappearance of [3H]resveratrol in circulation, and to study the distribution of resveratrol and its main metabolites among various organs including liver, kidney, brain, lungs, heart and spleen. In addition, the radiolabelled compounds present in plasma, urine and stool

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were analysed by HPLC using flow-through radioactivity and photodiode array detectors in order to distinguish between native resveratrol and its metabolites, and, if possible, to identify main resveratrol-derived compounds that either arise from cellular or colonic biotransformations.

Materials and methods

Chemicals

[3H]trans-Resveratrol was purchased from Moravek Biochemicals Inc. (Brea, CA, USA). Radiochemical purity was established by the supplier to be 99·8 % using HPLC analysis. Specific activity determined by MS was 133·2 GBq/mmol. Unlabelled resveratrol as well as all other chemicals were obtained from Sigma Chemical Co. (St Louis, MO, USA).

Animals and sample preparation

The study used 250 g male Sprague-Dawley rats obtained from the Comparative Biology Unit at the Royal Free & University College Medical School, and maintained on standard rat chow (Diet RM1, SDS Ltd, Witham, UK). Two groups of animals (n 6) were administered via gastric gavage, 50 mg/kg body weight resveratrol mixed with 1·85 MBq [3H]resveratrol and dissolved in 1 ml 50 % aqueous ethanol. Three additional rats were used as controls and received only 50 % aqueous ethanol. All animals were fasted for 4 h prior to resveratrol administration. All the procedures were conducted according to the guidelines set out in the UK Animals (Scientific Procedures) Act 1986.

At 2 or 18 h post-gavage, animals were anaesthetized by intraperitoneal injection of pentobarbitone sodium (90 mg/kg; Sagital; Rhone-Merieux, Harlow, UK). Then, 0·3 ml heparin (5000 IU/ml; CP Pharmaceuticals Ltd, Wrexham, UK) was injected via a tail vein to reduce blood clotting followed by removal of 2 ml blood by cardiac puncture into heparinized tubes. Animals were exsanguinated with 200 ml ice-cold heparinized 0·9 % (w/v) saline and organs were dissected out immediately. Plasma samples were separated by centrifugation at 600 g for 30 min. The haemoglobin concentrations of the cardiac blood sample and exsanguinated fluid were measured using a haemoglobin assay kit (Sigma, Poole, Dorset, UK) to allow calculation of blood volume as described previously (Abd El-Mohsen et al. 2004). The removed tissues, liver, kidneys, spleen, heart, small intestine, large intestine, lung and brain, were weighed and then homogenized in ice-cold 0·9 % (w/v) saline (10 vol./g tissue) using an Ultra Turrax homogenizer (Janke & Kunkel, Staufen, Germany) for 40 s. Urine and faeces from rats housed in metabolic cages were collected for the 18 h experiments. Intestinal contents were obtained by finger pressure and flushing with 0·9 % (w/v) saline alone. Samples were divided for either direct measurement of radioactivity by scintillation counting or frozen for subsequent extraction for HPLC analysis.

Measurement of radioactivity

Plasma (100 μl) or tissue homogenate (400 μl) was mixed with 4 ml Ultima Gold scintillation cocktail (Packard Biosciences, Beaconsfield, UK) designed to withstand quenching and to solubilize protein. Radioactivity was measured using a Packard Liquid Scintillation Counter (Tri-carb 2900TR) where counts were taken over a 5 min period and corrected for background. Data for organ weight and dpm of digested sample allowed calculation of organ content radioactivity. Percentage retention by each organ was then calculated. Percentage excretion was similarly determined in urine and faeces collected for 18 h following resveratrol administration.

Autoradiography was performed as previously described (Abd El-Mohsen et al. 2004) on tissue sections obtained from rats 2 h after gastric gavage of [3H]resveratrol.

Extraction of samples for HPLC analysis

Plasma (500 μl) was de-proteinized with 100 μl 20 % (w/v) TCA and then extracted with 500 μl ice-cold methanol. The extract obtained following centrifugation was evaporated to dryness under N and the residue dissolved in 500 μl 20 % (v/v) methanol in 1 % (w/v) acetic acid for quantitative HPLC analysis. Extraction of resveratrol and its metabolites from rat tissues was performed by mixing the homogenates with an equal volume of ice-cold methanol followed by vigorous vortexing for 1 min. The methanol extract obtained after centrifugation was dried under vacuum at 30°C by rotary evaporation and then the extracts were treated as described earlier. Urine samples were injected directly or after treatment with β-glucuronidase enzyme. This was done by mixing urine samples with an equal volume of sodium acetate buffer (pH 3·8) containing 12 000 U enzyme/ml and then incubated for 2 h at 37°C before analysis.

Quantitative determination of resveratrol and its metabolites was based on external standards. Calibration curves were conducted over the range 0·3–30 μM for plasma and tissue samples and were linear over the entire range with correlation coefficient values ≥ 0.995. Recovery experiments were performed to investigate the stability of both the unlabelled and the [3H]resveratrol under the conditions described.

HPLC analysis was performed on a Hewlett Packard Agilent 1100 system with a photodiode array detector (Model 1315A; Hewlett Packard) and Beta-RAM flow-through monitor (Model 3B; LabLogic Systems Ltd, Sheffield, UK). The samples were injected on to a Nova-pak C18 column (4·6 × 250 mm) fitted with a guard column (4·6 × 15 mm, 4 mm). Column temperature was set at 30°C. Injection volume was 100 μl for all samples. The mobile phase A consisted of methanol–water–5 M-HCl (5:94.9:0.1, by vol.) and mobile phase B of acetonitrile–water–5 M-HCl (50:49.9:0.1, by vol.). The gradient applied was as follows: from 0 to 5 min 100 % A; from 5 to 40 min to 50 % B; from 40 to 60 min to 100 % B; from 60 min to 65 min to 0 % B. Run time was 65 min followed by a 10 min delay prior to the next injection. Following UV detection, the eluate passed into the radiochromatography detector after mixing with the liquid scintillation cocktail (FlowLogic Max-Count; Lablogic Systems) in the ratio 1:3.

Resveratrol was initially identified using comparative retention times of pure standard and photodiode array spectra. The presence of glucuronide conjugates was confirmed (prior to liquid chromatography–MS/MS as described later) by incubating urine samples after β-glucuronidase treatment (as described earlier) and examining the decrease in the suspected

glucuronide peak and concomitant increase in the respective aglycone peak.

Liquid chromatography–MS analysis was performed using a Finnigan LCQ Deca XP quadrupole ion trap mass spectrometer. Separation was performed using a Phenomenex C18 column (2 mm × 5 mm) with the following gradient (phase A: 0·05 % (w/v) formic acid in water; phase B: 0·05 % (w/v) formic acid in acetonitrile). The liquid chromatography–MS gradient was 0–5 min 100 % A, 5–40 min from 100 % A to 50 % A, 40–60 min to 0 % A, 60–65 min 0 % A. Compounds were detected using a full ion scan and identified by performing product ion scans on selected ions.

Calculations and statistics

Values are given as means with their standard errors. Statistical analysis was performed using an unpaired *t* test (Instat) and considered significant at $P < 0.05$.

Results

Absorption and tissue distribution of radioactivity

In order to calculate the concentrations of [³H]resveratrol-derived radioactivity detected in different tissues and body fluids, the total counts of the administered dose was defined as 100 % (based on dpm) and the measured tissue levels were expressed as respective percentages of this total. Table 1 illustrates that at 2 h post-gavage, most of the recovered radioactivity, approximately 76·2 %, was still present in the gastrointestinal tract. At the same time-point, concentrations in plasma had reached only 1·7 % of the total dose administered, while the highest concentrations detected in tissues were found in liver and kidney and reached 0·98 % and 0·59 %, respectively. Only trace amounts of radioactivity (< 0·1 % of administered dose) were detected in the brain, lungs, heart and spleen, with the aggregate value for all the tissues investigated being < 2 %.

Repeating the dosing paradigm described earlier, with the exception that all plasma and tissue samples were collected at 18 h post-[³H]resveratrol administration, the following results were obtained. The concentrations of [³H]resveratrol-derived radioactivity detected in plasma represented only

0·48 % of the total dose administered, whereas the sum of all measured tissue doses reached only 0·35 % of the total dose ingested (Table 1). Adding the radioactivity concentrations of plasma and organs as well as the concentrations measured in the content of the gastrointestinal tract (approximately 5·1 % total dose), the urine (approximately 3·3 % total dose) and the excreted faeces (approximately 1·6 % total dose), approximately 11 % total dose administered was accounted for at 18 h post-administration.

If absorption is measured as the difference between the total counts gavaged and the total amount recovered in the stool (18 h faeces plus gastrointestinal tract content), it appears that almost 90 % of the administered resveratrol was absorbed inside the body over the 18 h period. Surprisingly, the concentrations detected in urine, which would represent a part of the absorbed (and subsequently excreted) resveratrol, were only 3·3 %. The undetected radioactivity is likely to reflect loss via perspiration or respiratory water and/or the accumulation of a high proportion of the administered resveratrol in other tissues, such as skeletal muscle and adipose tissue. Such tissues were not examined in the present study, as we were primarily interested in the tissue concentrations and disposition of metabolites in organs relevant to the major degenerative diseases (i.e. heart, liver and brain).

Although the liver and kidneys had the highest concentrations at 2 h (Fig. 1), the amount detected at 18 h reached only around 10 and 25 %, respectively, of what was detected at 2 h. In contrast, although the brain initially contained trace amounts of the administered dose, 43 % of the concentrations detected at 2 h were also recovered at 18 h.

Autoradiography demonstrated the presence of ³H-activity within the blood vessels of all organs investigated, but not within most organ-specific cells (Fig. 2). In addition, silver grains representing the presence of ³H were demonstrated within the tubular fluid in the kidney and intervillus space in the small intestine.

Identification of resveratrol metabolites in rat tissue extracts

The chemical nature of the [³H]*trans*-resveratrol-derived radioactivity detected in rat plasma and various tissues was investigated using HPLC analysis with photodiode array and radioactive detection (Fig. 3, left and right panels, respectively). The analysis of a mixture of authentic, unlabelled resveratrol and native [³H]*trans*-resveratrol demonstrated that the test compound elutes at a retention time of 43·5 min, and that this peak has the characteristic UV spectrum of resveratrol (peak 2; Fig. 3(a)). Plasma extracts obtained from animals 2 h after dosing with [³H]*trans*-resveratrol revealed a peak with the same spectral and chromatographic characteristics as the authentic standard (peak 2), and was thus assigned to be aglyconic resveratrol. In addition, a major peak possessing a resveratrol-like UV spectrum, but a retention time of 36·2 min (peak 1; Fig. 3(c)), could be identified. With a retention time that is 7 min shorter as compared with native resveratrol, peak 1 is more hydrophilic than the native test compound, thus it was hypothesized to represent a resveratrol *O*-glucuronide. HPLC profiles for control samples obtained from animals that did not ingest resveratrol did not exhibit either peak 1 or peak 2 (Fig. 3(b)).

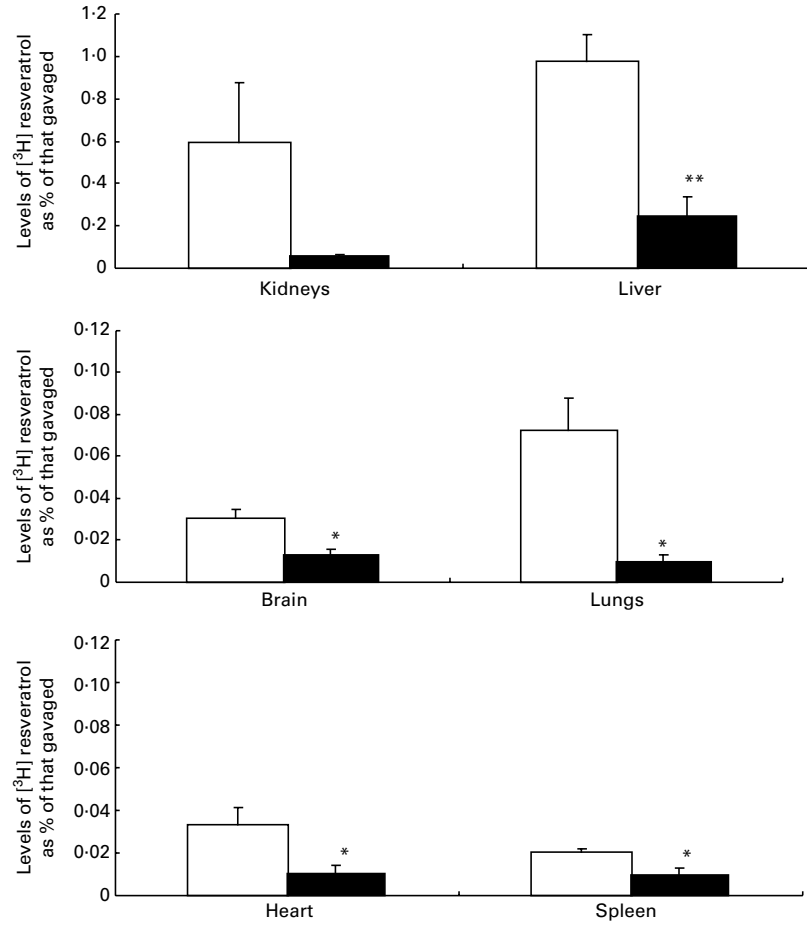**Table 1.** Concentrations of [³H]*trans*-resveratrol-derived radioactivity detected 2 and 18 h post-gavage†

Mean values with their standard errors (six rats per group)

|	2 h		18 h	
	Mean	SEM	Mean	SEM
Tissues	1·7	0·44	0·35*	0·11
Plasma	1·7	0·25	0·48**	0·05
Gastrointestinal tract	76·2	8·8	5·1**	1·04
Urine	–		3·3	0·01
Faeces	–		1·55	0·28
Total radioactivity recovered	79·6	9·5	10·7**	1·5

Mean values were significantly different between 2 and 18 h (unpaired *t* test): *$P < 0.05$; **$P < 0.001$.

† The total counts of the administered dose was defined as 100 % (based on dpm) and the measured tissue concentrations were expressed as respective percentages of this total.

Fig. 1. Concentrations of [³H]*trans*-resveratrol in rat tissues at 2 h (□) and 18 h (■) after gastric gavage. The total count of the administered dose was defined as 100 % (based on dpm) and the measured tissue levels were expressed as respective percentages of this total. For details of procedures, see p. 63. Values are means with their standard errors depicted by vertical bars (six animals per group). Mean values were significantly different between 2 and 18 h: *$P<0.05$; **$P<0.001$.
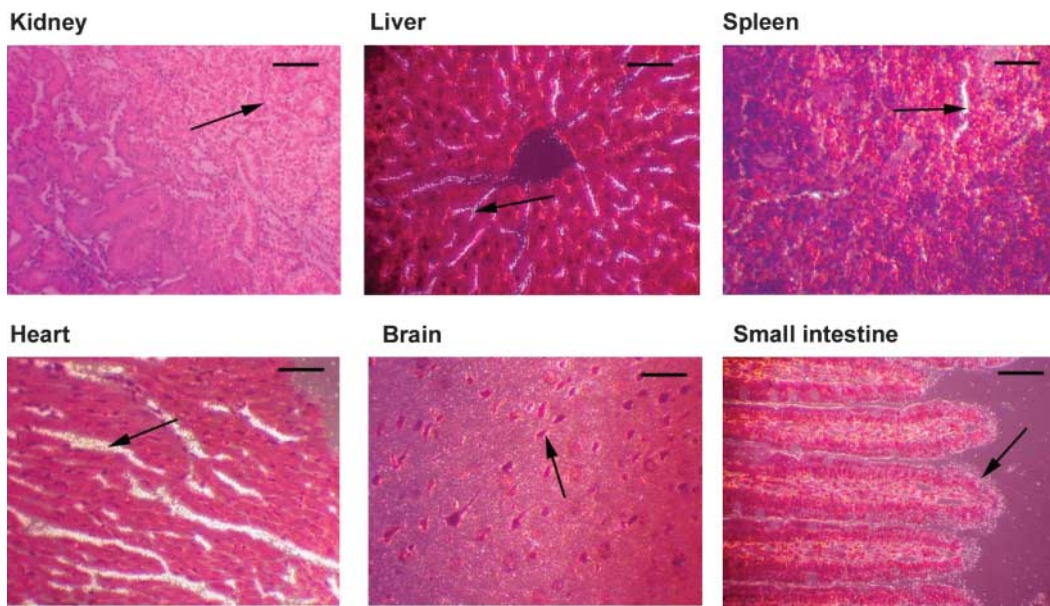
Fig. 2. Autoradiographs of tissue sections obtained from rats 2 h after gastric gavage of [³H]*trans*-resveratrol. Tissues have been counterstained with haemotoxylin and eosin. Silver grains representing the presence of ³H-activity within blood vessels in all tissues plus tubular fluid in the kidney and intervillus space in the small intestine are shown (→). Scale bars = 50 μm. For details of procedures, see p. 63.
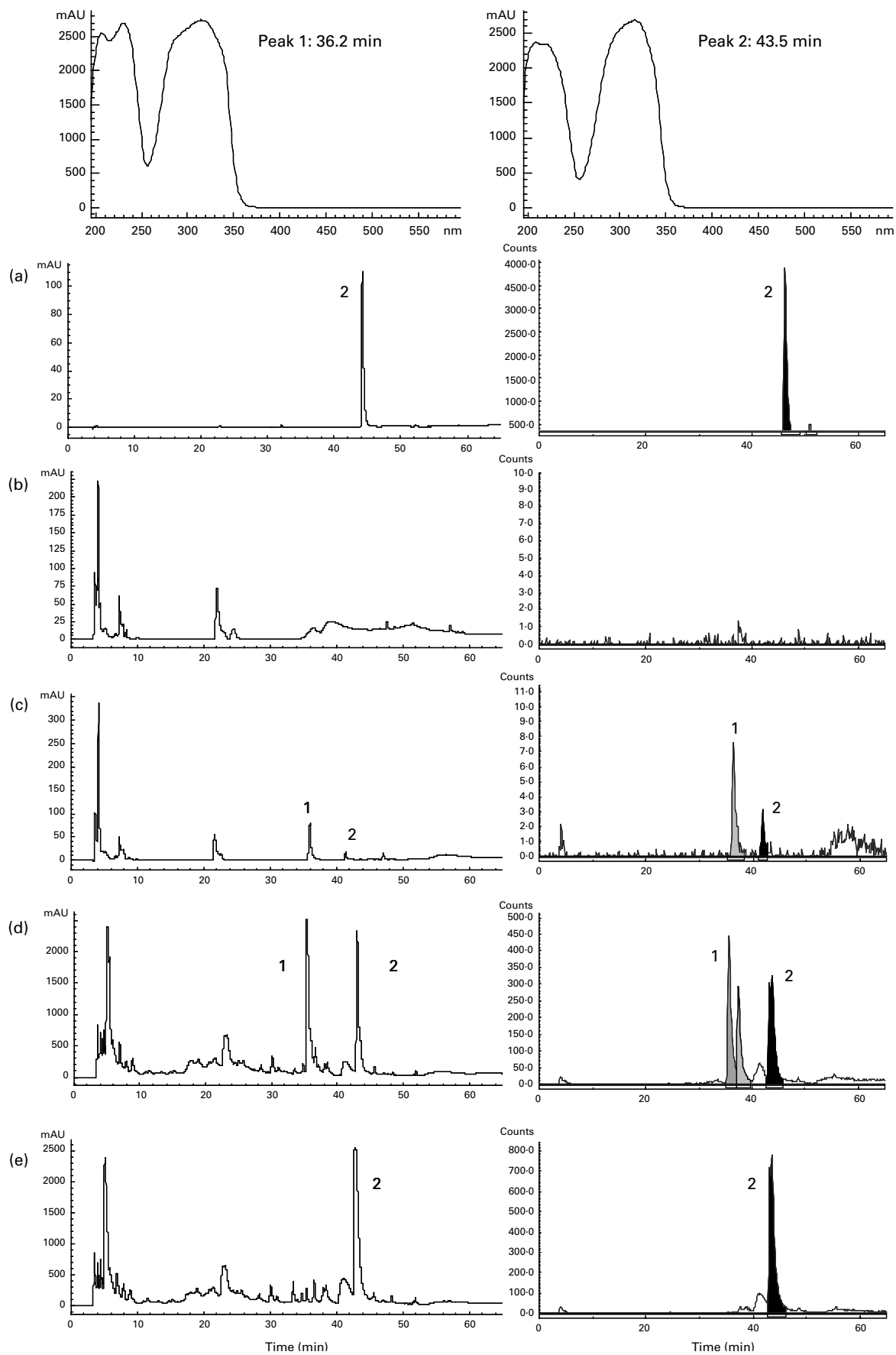
Analyses of urine samples (Fig. 3(d)) also identified two major radioactive peaks, one of which was identical to aglyconic resveratrol (peak 2). However, peak 1 appeared to consist of two radiolabelled compounds co-eluting at the same retention time. Thus it may be assumed that peak 1 represents two compounds with closely related structures. Treatments of urine with β-glucuronidase resulted in the disappearance of peak 1, and a corresponding increase was observed in the resveratrol aglycone peak (peak 2; Fig. 3(e)), which strongly supports the hypothesis that peak 1 represented two resveratrol-O-glucuronides, potentially derivatized on either position 3 or 5 of the trans-resveratrol molecule. Importantly, no other signals on the UV trace or on the radioactive chromatogram were observed, indicating that no other major [3H]resveratrol-derived metabolites were present.

Liquid chromatography–MS analysis confirmed the identity of resveratrol (peak 2) and its O-glucuronides (Fig. 4). Resveratrol is identified by comparison with the retention time of the authentic standard and the fragmentation reaction m/z $229 \rightarrow m/z$ 135. A signal, assigned to the glucuronide, with the predicted molecular weight (404 Da) and an expected fragment (neutral loss of glucuronic acid, 176 Da) could be detected in urine, plasma and small intestine cell extracts. None of these signals was found in the control samples.

Concentrations of resveratrol metabolites at 2 and 18 h were calculated in plasma and tissues based on UV-absorption peaks as assessed using a photodiode array detector, and calculated using the area under the curve for each peak, respectively. All analyses were based on calibration curves established using different concentrations of authentic, unlabelled trans-resveratrol. Fig. 5 shows resveratrol/metabolite concentrations expressed as nmol/ml plasma or g tissue. In a similar manner to the radioactive detection, the total concentration of resveratrol aglycone and its glucuronide declined at 18 h compared with 2 h. It was clear that total measurement of radioactivity using scintillation counting was a more sensitive tool since the concentrations of metabolites at 18 h was below the detection limit in some tissue samples following injection on to the HPLC system. In all tissue and plasma samples obtained at 2 h post-gavage, resveratrol glucuronide was the only major metabolite. Plasma concentrations of resveratrol glucuronide reached 7 μM at 2 h but disappeared completely at 18 h. A similar picture was observed in the kidney; however, in the liver, heart, lungs and the brain, the detected metabolite at 18 h was mainly the aglycone.

Discussion

In the present study, we have studied the distribution of trans-resveratrol, a dietary stilbene, in rat tissues following oral administration. In particular, we have assessed the fate of 3H-labelled resveratrol and investigated the chemical nature of its metabolites.

The amounts of radioactivity found in plasma and tissues 2 h after resveratrol gavage were relatively low, with almost all the radioactivity in the intestinal tract. These observations are consistent with previous studies, during which resveratrol was orally administered to rats (Soleas et al. 2001; Vitrac et al. 2003). The disappearance of radioactivity from the gastrointestinal tract after 18 h, and the very low levels measurable in the faeces, support the previous suggestion that the faecal route is a minor way of elimination (Vitrac et al. 2003). Failure to account for the total administered radioactivity might be caused by retention of resveratrol in tissues such as skeletal muscle, skin, bone and adipose tissues. This is acceptable based on the fact that these tissues account for 80 % of the animal weight.

Resveratrol-O-glucuronides have been previously identified in rat plasma after the oral administration of the aglycone (Marier et al. 2002; Yu et al. 2002). In agreement, our analyses showed that the major metabolite in the plasma was the glucuronide conjugates reaching concentrations of 7 μM. This is comparable to studies in man where plasma values obtained were ranging between 2 and 4 μM following the intake of 25 mg pure resveratrol (Walle et al. 2004) or 600 ml red wine (Vitaglione et al. 2005). The absence of O-sulphated resveratrol conjugates in the present experiments is in agreement with a recent study describing the effect of the administered dose on the nature of resveratrol metabolites (Wenzel et al. 2005). Wenzel et al. (2005) propose that O-sulphation via O-sulphotransferases is a secondary elimination pathway only supporting O-glucuronidation when a high dose of resveratrol is administered to animals.

In accordance with the present results, micro-autoradiographic evidence of the distribution of resveratrol-derived radioactivity in the rat liver and kidney was previously demonstrated (Vitrac et al. 2003), but no data on the chemical nature of this radioactivity were provided. The predominance of conjugated resveratrol in plasma at 2 h would suggest that these derivatives are also more likely to reach the tissues. However, contradictory reports exist on the possibility that resveratrol glucuronide is the biologically active form of resveratrol. Resveratrol was reported to be more potent in blocking the function of the aryl hydrocarbon receptor (required for the conversion of proximal carcinogens to metabolites) when administered to rats than when incubated with cell cultures in vitro, implying the biological activity of metabolites (Casper et al. 1999; Soleas et al. 2001). On the other hand, the glucuronides possessed no cytotoxic or antiviral activities compared with the potent anti-HIV activity of the parent compound resveratrol when tested in cell culture experiments using human peripheral blood mononuclear cells (Wang et al. 2004).

The present results showed that 2 h following the administration of resveratrol, while the liver and kidneys retained only the glucuronide, in other tissues such as the lungs and brain, detectable levels of the aglycone were found. Moreover, more tissues, including the liver, retained a higher ratio of the aglycone to the glucuronide at 18 h post-gavage compared with their ratio at 2 h. Due to the absence of resveratrol

Fig. 3. HPLC detection of resveratrol and its metabolites using UV-detection at 290 nm (left panels) and 3H-detection (right panels). For details of procedures, see p. 63. (a), Standard resveratrol; (b), control plasma extract; (c), plasma extract from rats 2 h after resveratrol gavage; (d), urine collected for 18 h after resveratrol gavage; (e), post-enzymatic urine sample collected for 18 h after resveratrol gavage. AU, absorbance units; peak 1, resveratrol glucuronide; peak 2, resveratrol. UV spectra (200–600 nm) are shown at the top.
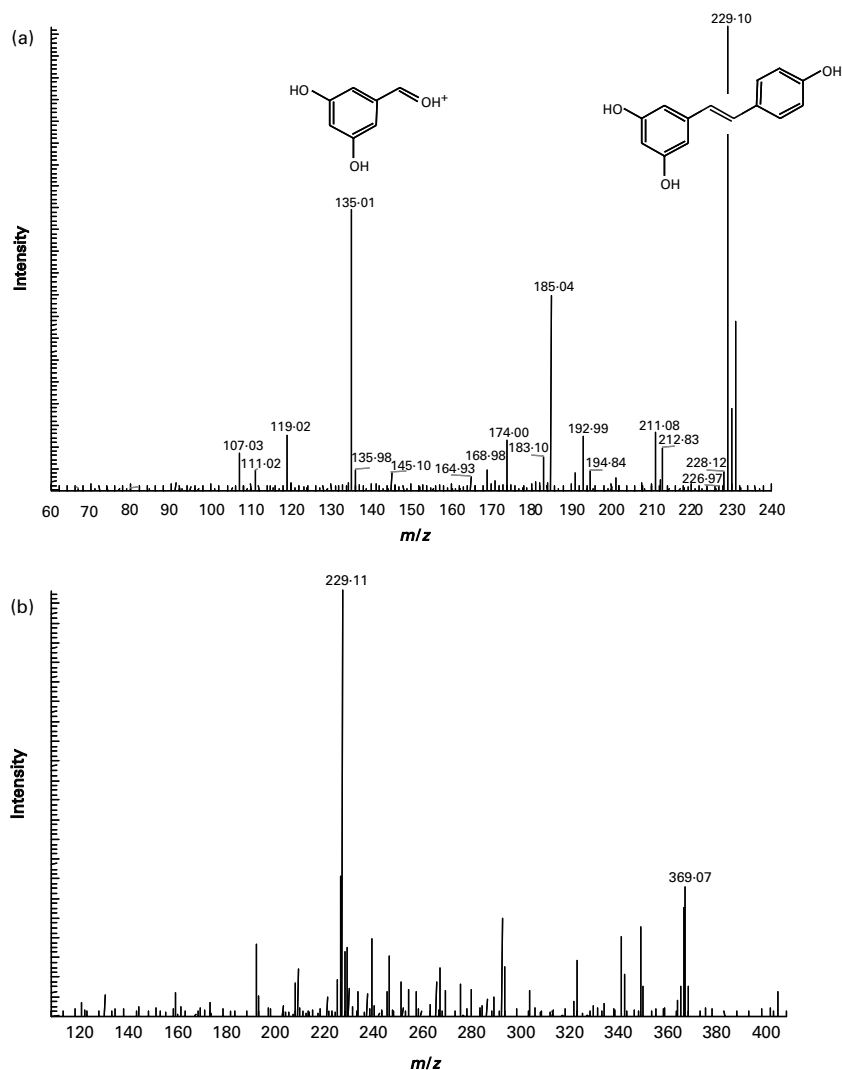
Fig. 4. MS/MS spectrum of resveratrol (a) and its glucuronide (b) obtained from rat plasma after oral gavage of 50 mg resveratrol/kg. Resveratrol is identified by the retention time of the standard and the fragmentation reaction m/z 229 → m/z 135 (possible structure shown). The glucuronide is identified by the neutral loss of glucuronic acid (m/z 405 → m/z 229). The peak at m/z 369·07 results from the loss of two water molecules off the glucuronide. For details of procedures, see p. 63.

aglycone in the plasma, the present results support the possibility that the ubiquitously existing β-glucuronidase could convert the metabolites back to resveratrol locally or systemically. Alternatively, the preferential uptake of the aglycone form into cells could lead to its localization in tissues, i.e. heart, even though it was undetectable in plasma.

The radioactive concentrations detected in plasma and tissues 18 h after [3H]resveratrol administration were considerably lower than at the 2 h time-point, especially in the kidneys where concentrations dropped to 10 % of that detected at 2 h. This indicates that renal excretion might be the major way of elimination of the 3H-label, an observation supported by the high radioactive concentrations found in urine. In our previous study with naringenin (Abd El-Mohsen *et al.* 2004), high excretion was observed in the urine, nevertheless, radioactivity accumulating in tissues increased over time, suggesting the existence of other slowly absorbed metabolites. It is possible that resveratrol possess faster excretion and hence less tissue retention. However, if indeed resveratrol was subjected to further metabolism, it is logical to assume

that these metabolites carrying the 3H-label will be excreted in urine. Interestingly, dihydroresveratrol was reported as a urinary metabolite following the oral ingestion of resveratrol in human subjects (Walle *et al.* 2004). Our urinary excretion data showing the absence of this metabolite in rat urine indicate differences in the metabolic pathway responsible for the formation of such a metabolite in man.

Associations between the urinary excretion of simple phenolics such as hydroxyhippuric acid and hydroxyphenylacetic acid and high flavonoid intake have also been observed through a number of human studies on the metabolism of dietary polyphenols (Bravo *et al.* 1994; Gross *et al.* 1996; Rechner *et al.* 2001, 2002). In our previous studies, 3-(4-hydroxyphenyl) propionic acid and *p*-hydroxbenzoic acid were detected in urine following gavage of naringenin and pelargonidin to rats, respectively (Abd El-Mohsen *et al.* 2004, 2005). Contrary to that, with resveratrol, urine samples did not show any radioactive peaks, which could be attributed to phenolic degradation products. The present results show that resveratrol does not serve as a substrate for enzymes of colonic
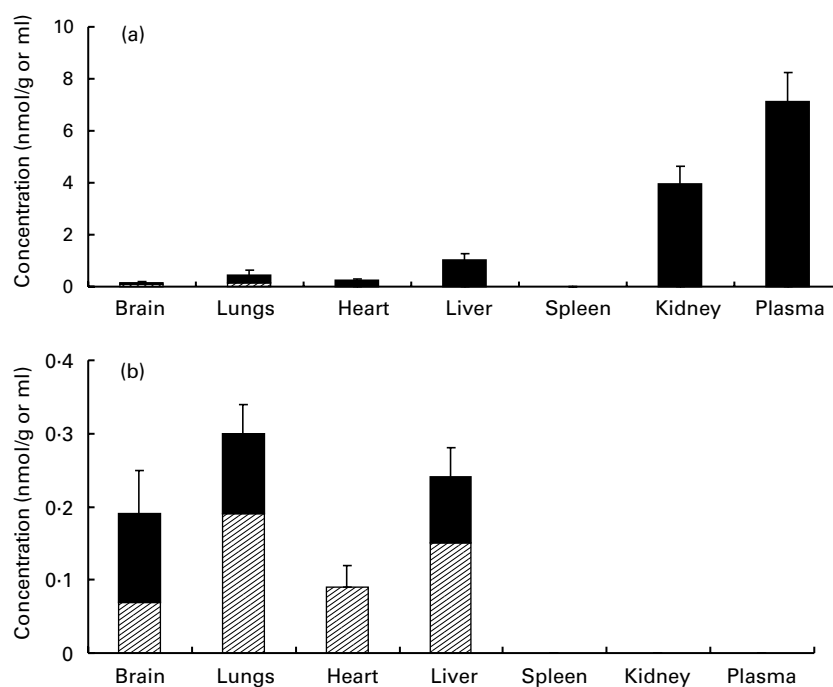
Fig. 5. Concentrations of resveratrol (▨) and its metabolites (■) in plasma and tissues obtained 2 h (a) and 18 h (b) after gastric gavage of 50 mg resveratrol/kg. For details of procedures, see p. 63. Values are means with their standard errors depicted by vertical bars (six animals per group).

microflora, possibly due to the absence of the C ring and the high stability of the *trans*-stilbene structure (Trela & Waterhouse, 1996).

In summary, the present study provides well-characterized data of the metabolic fate of resveratrol through the use of HPLC with on-line radioactivity detection. The present data indicate that there are no phenolic degradation products formed following resveratrol consumption, suggesting that resveratrol is not subject to degradation by large intestinal bacteria. Furthermore, whilst the glucuronide is the predominate form in the plasma, resveratrol aglycone may represent the main form present in the tissues. The present study provides additional information about the nature of resveratrol metabolites and which forms might be responsible for its *in vivo* biological effects.

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