Vascular deconjugation of quercetin glucuronide: The flavonoid paradox revealed?

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Scope: The dietary flavonoid quercetin exerts protective cardiovascular effects. Because quercetin is rapidly metabolized into less active or inactive glucuronidated metabolites and the plasma concentrations of free quercetin are very low, a huge amount of scientific data generated along decades with the unconjugated compounds in vitro has been questioned. We aimed to determine whether glucuronidated quercetin can deconjugate in situ and whether deconjugation leads to a biological effect.

Methods and results: Quercetin and quercetin-3-O-glucuronide (Q3GA) were perfused through the isolated rat mesenteric vascular bed. Quercetin was rapidly metabolized in the mesentery. In contrast, the decay of Q3GA was slower and was accompanied by a progressive increase of quercetin in the perfusate and in the tissue over 6 h, which was prevented by the β-glucuronidase inhibitor saccharolactone. Incubation of mesenteric arterial rings mounted in a wire myograph with Q3GA for ≥1 h resulted in a significant inhibition of the contractile response which was also prevented by saccharolactone. Moreover, the intravenous administration of Q3GA resulted in a slow onset and sustained blood pressure lowering effect, demonstrating for the first time that Q3GA has effects in vivo.

Conclusion: We propose that Q3GA behaves as a quercetin carrier in plasma, which deconjugates in situ releasing the aglycone which is the final effector.

Keywords:
Blood pressure / Glucuronide / Metabolism / Quercetin / Vasodilation

1 Introduction

Quercetin is the most abundant and widely distributed flavonoid, a class of phenolic compounds consumed in the diet in fruits, vegetables, nuts and derived products such as red wine and chocolate. Prospective epidemiological studies have shown an inverse correlation between dietary flavonoid intake and mortality from coronary heart disease [1–3]. These data are supported by multiple animal studies showing that quercetin and related flavonoids exert a wide range of biological effects both in vitro and in vivo [4]. Thus, they induce systemic and coronary vasodilatation and anti-aggregant effects in vitro [5–9] and reduce blood pressure, the oxidative status and the end-organ damage in animal models of hypertension [10].

One of the main difficulties in understanding the biological activity in vivo of flavonoids is their low concentration.

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in plasma where they are found as conjugated derivatives different to the forms present in food (i.e. β-glycosides and less frequently aglycones). β-Glycosides are mostly hydrolyzed in the intestines into the aglycones, which once absorbed are rapidly conjugated with glucuronic acid and/or sulfate during first-pass metabolism (intestine-liver) and a portion of the metabolites are also methylated [11–13]. Because the plasma concentrations of free quercetin and related flavonoids are very low, a huge amount of scientific data generated along decades [14] with the unconjugated compounds in vitro has been questioned [15, 16]. Recent studies have shown that the major metabolites of quercetin in human plasma (quercetin-3-O-glucuronide [Q3GA], quercetin-3′-O-sulfate and isorhamnetin-3-O-glucuronide) show a much weaker in vitro effect, if any, than the parent compounds [17–20]. To our knowledge, the effects in vivo of the metabolites have not been analyzed so far.

We hypothesized that (i) Q3GA can deconjugate in situ, (ii) Q3GA exerts its effects in vitro via the release of quercetin and (iii) Q3GA exerts a blood pressure lowering effect.

2 Materials and methods

2.1 Animals

The present study was conducted according to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication no. 85–23, revised 1996) and approved by our Institutional Committee (Comité de Experimentación animal, Universidad Complutense #3011061) for the ethical care of animals. Male Wistar rats (250–300 g) were obtained from Harlan Laboratories.

2.2 Materials and solutions

Q3GA was isolated from green bean pods and stored as described [21] and all other drugs and chemicals were purchased from Sigma (St. Louis, MO, USA). Quercetin was purchased from Sigma (St. Louis, MO, USA). Quercetin was isolated from green bean pods and stored as described [21] and all other drugs and chemicals were purchased from Sigma (St. Louis, MO, USA). Quercetin was dissolved in dimethyl sulfoxide (DMSO), and all the other compounds were dissolved in distilled, deionized water. The Krebs solution contained 118 mM NaCl, 4.75 mM KCl, 25 mM NaHCO₃, 1.2 mM MgSO₄, 2 mM CaCl₂, 1.2 mM KH₂PO₄, and 11 mM glucose. The HEPES-buffered solution contained 130 mM NaCl, 5 mM KCl, 1.2 mM MgCl₂, 10 mM glucose and 10 mM HEPES (pH adjusted to 7.4 with NaOH).

2.3 Isolated perfused mesentery of the rat

The isolated perfused mesentery of the rat was prepared as described [22]. Briefly, male albino Wistar rats were sacrificed, the abdomen opened and the ileocolic and colic branches of the superior mesenteric artery ligated. The superior mesenteric artery was cannulated and the superior mesenteric vascular bed perfused for 5 min (2 mL/min) with HEPES buffer. Then, the intestine was separated from the mesentery and the preparation supported on an organ bath and the arteries perfused at a constant flow of 2 mL/min with warmed (37°C) HEPES buffer in a closed system with a total volume of 7 mL of HEPES buffer. After 5 min, quercetin or Q3GA were added to this recirculated-HEPES buffer in the absence or the presence of the β-glucuronidase inhibitor d-saccharolactone (300 μM) [23] or vehicle. Samples of 150 μL of the recirculated Krebs were taken at different time points and after 3 or 6 h, the mesenteric vascular bed was frozen at the end of the experiment for further analysis.

2.4 Extraction of quercetin and metabolites from mesenteric bed and the recirculated buffer

The homogenized mesenteric bed (0.5 mL) was macerated in 0.5 mL methanol/water (60:40, v/v) for 30 min at 25°C in an ultrasonic bath and then centrifuged for 5 min at 3500 × g. The supernatant was collected and the pellet subjected to additional extraction with 1 mL methanol assisted by sonication (1 min) using a Labsonic 1510 ultrasonic device (Braun, Germany). The suspension was centrifuged and the pellet subjected to the process with methanol further two times. All supernatants were combined and evaporated in a centrifugal concentrator micVac (GeneVac, Ipswich, UK). The residue was dissolved in 250 μL acetonitrile/water (30:70 v/v) and centrifuged (5 min, 3500 × g) previous to its injection (100 μL) in HPLC-DAD-ESI/MS. The perfusion fluid was filtered through 0.45-μm PVDF (polyvinylidene difluoride membrane) Whatman 4-mm syringe filters (Whatman International, Maidstone, UK) and directly injected (100 μL) in HPLC-DAD-ESI/MS.

2.5 HPLC-DAD-ESI/MS analyses

Analyses were carried out in a Hewlett-Packard 1100 chromatograph (Agilent Technologies, Waldbronn, Germany) with a quaternary pump and a diode array detector (DAD) coupled to an HP Chem Station (rev. A.05.04) data-processing station. An Ascentis™ RP-Amide 3 μm (2.1 x 150 mm) column was used at a temperature of 30°C. The solvents used were (A) 0.1% formic acid and (B) ACN. An elution gradient was established from 15 to 50% B over 15 min, isocratic 50% B for 10 min, from 50 to 75% B over 3 min, isocratic 75% B for 10 min, and re-equilibration of the column, at a flow rate of 0.2 mL/min. Double online detection was carried out in the DAD using 370 nm as a preferred wavelength and in a mass spectrometer (MS) connected to HPLC system via the DAD cell outlet.
Quantitative analysis of the assayed flavonols and conjugated metabolites was performed from their chromatographic peaks recorded at 370 nm by comparison with calibration curves obtained by injection of increasing concentrations of quercetin and Q3GA. Chromatograms were also recorded at 280 nm in order to detect and quantify protocatechuic acid. MS detection was performed in an API 3200 Qtrap (Applied Biosystems, Darmstadt, Germany) equipped with an ESI source and a triple quadrupole-ion trap mass analyzer that was controlled by the Analyst 5.1 software. Zero-grade air served as the nebulizer gas (30 psi) and turbo gas for solvent drying (400°C, 40 psi). Nitrogen served as the curtain (20 psi) and collision gas (medium). The quadrupoles were set at unit resolution. The ion spray voltage was set at −4500 V in the negative mode. Precursor ion analysis was employed to detect all the precursor ions that fragment to a common product ion (i.e. m/z 301 corresponding to quercetin). Settings were used as follows: declustering potential (DP) −40 V, entrance potential (EP) −10 V, collision energy (CE) −50 V, and cell exit potential (CXP) −3 V. Enhanced product ion (EPI) mode was further performed in order to obtain the fragmentation pattern of the parent ion(s) of the studied transition in the previous experiment using the following parameters: DP −50 V, EP −6 V, CE −25 V, and collision energy spread (CES) 0 V.

2.6 β-Glucuronidase activity and protein and mRNA expression

β-Glucuronidase activity was measured by a colorimetric analysis using phenolphthalein mono-β-glucuronide as the substrate [24]. Briefly, 30 μg of protein of vascular mesenteric bed homogenates were mixed with 0.6 mM phenolphthalein mono-β-glucuronide in 100 μL of 0.1 mM sodium phosphate buffer pH 5. After incubation at 37°C for 30 min followed by adding 200 μL of 0.1 M sodium phosphate buffer, pH 11, the absorbance at 540 nm indicating the formation of phenolphthalein aglycone was measured. In some experiments, β-saccharolactone (1 mM) was added 1 h before phenolphthalein mono-β-glucuronide addition. The protein expression of β-glucuronidase was analyzed by Western blot. Briefly, small mesenteric artery homogenates were run on a SDS-polyacrylamide electrophoresis. Proteins were transferred to polyvinylidene difluoride membranes and incubated with primary polyclonal rabbit anti-β-glucuronidase (SantaCruz Biotechnology, Santa Cruz, CA, USA) overnight and with the corresponding secondary peroxidase conjugated antibody. Antibody binding was detected with an ECL system (Amersham Pharmacia Biotech, Amersham, UK). For quantitative reverse transcriptase-PCR (RT-PCR) analysis, total RNA was extracted from small mesenteric arteries and reverse transcribed to cDNA by standard methods, PCR was performed with a Techne Techgene thermocycler (Techne, Cambridge, UK) using the primers for β-glucuronidase sense, 5’-CATGAC GAACCGATCACCCAC-3’, and antisense, 5’-ACGGTCTGCT TCCCATACAC-3’.

2.7 Effects in mesenteric resistance arteries and in the aorta

Endothelium-intact aortic or mesenteric arterial rings (internal diameter 2 and 0.3–0.6 mm, respectively) were mounted in a conventional organ bath or in a wire myograph, respectively, in Krebs solution and stretched to 2 g (aorta) or to give an equivalent transmural pressure of 100 mmHg (mesenteric arteries). In some experiments, the endothelium was removed by intraluminal perfusion of a small mesenteric artery with 0.5% 3-[3-cholamidopropyl]dimethyl-ammonio]-1-propanesulfonate (CHAPS) for 30 s followed by repeated washing with normal Krebs solution. The presence of functional endothelium was assessed in all preparations by the ability of acetylcholine (1 μM) to induce more than 50% relaxation of vessels maximally precontracted with norepinephrine. Vessels were considered to be denuded of functional endothelium when there was no relaxation response to acetylcholine. In the mesenteric arteries, after equilibration, Krebs solution was exchanged with a high-potassium Krebs solution (80 mM) for 15 min. After removing the high potassium solution, concentration–response curves to phenylephrine were constructed by cumulative addition of the drugs. After washing phenylephrine, rings were exposed to quercetin (100 μM), quercetin-3-glucuronide (10, 25, 100 μM), quercetin-3-glucuronide 100 μM, β-saccharolactone (300 μM, added 1 h before) or vehicle (DMSO) in parallel experiments for 30, 60, 120 or 180 min and then response curves to phenylephrine were repeated. In these experiments, the contractile responses to phenylephrine after incubation with different drugs were expressed as a percentage of maximal response in the first exposure to phenylephrine. In some experiments, the effects of quercetin or Q3GA were assessed in mesenteric arteries incubated with nitro-arginine methylester (L-NAME, 100 μM) for 20 min. The aorta or the mesenteric arteries were exposed to phenylephrine and exposed to cumulative increases in protocatechuic acid. In some experiments, aortic rings exposed to quercetin were then washed in quercetin-free buffer to analyze the recovery of the effect of quercetin.

2.8 Effects on blood pressure

Rats were anaesthetized with 2.5 mL/kg equitensin (500 mL contain 43% w/v chloral hydrate in 81 mL ethanol; 4.86 mg nembutal; 198 mL propylene glycol; 10.63 g MgSO₄; distilled water) (i.p.) and the carotid artery was cannulated to obtain direct measurements of arterial blood pressure. The catheter was exteriorized through the skin on the dorsal side of the neck and protected with a silver spring. A cannula was also
introduced into the left jugular vein for the administration of quercetin metabolites. Upon completion of the surgical procedure, rats were fasted and allowed to recover for 6 h and, after connecting the catheter to a transducer and a recorder (TRA-021 and Letigraph 2000, respectively; Letica SA, Barcelona, Spain), blood pressure and heart rate were continuously recorded.

2.9 Statistical analysis

The results are expressed as the mean ± SEM and n reflects the number of experiments in tissues from different animals. Statistically significant differences between experimental groups were calculated by Student’s t-test for paired or unpaired observations. For multiple comparisons, a linear univariate analysis (multiple way ANOVA) was carried out and when differences were significant, pairwise comparisons were carried out. p < 0.05 was considered statistically significant.

3 Results

3.1 Metabolism of quercetin at the perfused mesenteric bed

After 5 min of recirculating a total volume of 7 mL of Krebs buffer (4 mL of reservoir + approximately 3 mL of dead space of tubes and tissue) through the mesenteric bed at 2 mL/min, quercetin was added to the reservoir at the final concentrations of 10, 30 and 100 μM. In the first sample, taken at 10 min at the reservoir (time enough for full mixing of the reservoir content with the dead space and tissue), 50–90% of the quercetin added could no longer be detected (Fig. 1). A second slower phase (10–180 min) of decay could be fitted to an exponential decay, indicative of first-order kinetics (Fig. 1B). The rate constants of this process were similar for the three concentrations tested (0.37 ± 0.25 × 10⁻³, 0.40 ± 0.02 × 10⁻³ and 0.34 ± 0.05 × 10⁻³ s⁻¹ for 10, 30 and 100 μM, respectively). Thus, the half-life of quercetin in this second process was 32 ± 3 min. However, at 180 min, low but clearly detectable concentrations of quercetin

Figure 1. Metabolism of quercetin at the perfused mesenteric bed. (A) HPLC chromatograms recorded at 280 nm of samples taken from the recirculated buffer at 10 and 180 min after the addition of quercetin (100 μM). The inset shows the mass and UV spectra of protocatechuic acid. (B) Exponential decay of quercetin added at 10, 30 and 100 μM in the recirculate. (C) Protocatechic acid appeared at 10 min in amounts comparable to the added quercetin at sample of the recirculate. The results are expressed as mean ± SEM of three to six experiments.
could still be detected in the recirculated buffer. Glucuronidated or sulfated metabolites of quercetin were not found in any experiment. Protocatechuic acid was quantitatively the major metabolite, which appeared early (at 10 min) and in concentrations of the same order of those of the added quercetin (Fig. 1C). Incubation of quercetin for periods of up to 3 h with the Krebs solution previously recirculated for 15 min through the mesentery (conditioned Krebs) did not result in any metabolite, ruling out that metabolism could occur via enzymes released from the mesentery as has been shown with some proteases [22]. Despite the low levels of quercetin in the recirculated buffer, after 180 or 360 min quercetin could be detected in the homogenates of the mesentery in a concentration-dependent manner (Fig. 2). In most experiments, methylquercetin (3′- or 4′-) was also present in these homogenates, while protocatechuic acid was not found (Fig. 2).

3.2 Metabolism of quercetin-3-glucuronide at the perfused mesenteric bed

At 10 min after the addition of Q3GA, ~60% of Q3GA (e.g. ~60 μM from 100 μM added) remained in the recirculated buffer; the missing 40% probably reflects uptake by the tissue. However, Q3GA was relatively stable in the recirculated buffer (Fig. 3) with a half-life (~225 min) much more prolonged than that of quercetin. This decay was accompanied by a progressive increase in quercetin in the recirculated buffer. Despite quercetin being present in significant concentrations in the recirculated buffer, protocatechuic acid was not found in these experiments. To corroborate quercetin deconjugation, experiments were performed with Q3GA in the presence of the β-glucuronidase inhibitor saccharolactone. Accordingly, this drug fully prevented the decay in Q3GA and the increase in quercetin (Fig. 3C). The analysis of the homogenates of the mesentery recirculated with Q3GA (Fig. 4) showed that after 180 min, the concentration of Q3GA was low but a significant peak of quercetin together with a minor peak of methylquercetin could be detected. At 360 min, a further decrease in Q3GA and the corresponding increase in free quercetin were observed. As expected, in the presence of saccharolactone a larger amount of Q3GA was preserved in the mesentery and consequently a decreased level of free quercetin was found.

3.3 β-Glucuronidase activity and expression

As shown in Fig. 4E, β-glucuronidase activity sensitive to saccharolactone was detected in homogenates of the mesenteric bed. Moreover, the expression of the protein was...
also observed in Western blots (Fig. 4E) and mRNA expression was confirmed by quantitative PCR (not shown).

3.4 Effects on vascular contraction

In the mesenteric arteries incubated for 30 min with Q3GA (100 µM), there was no significant effect on the contractile response induced by phenylephrine while quercetin induced a strong inhibitory effect (Fig. 5A). However, a longer incubation period of 180 min resulted in a significant inhibitory effect of Q3GA (Fig. 5B), which was completely inhibited in the presence of saccharolactone (Fig. 5C). The presence of the NO (nitric oxide) synthase inhibitor L-NAME or the removal of endothelium had no major effect on the inhibitory effects of Q3GA (Fig. 5D–F). Figure 6 shows the time course of the effects of lower concentrations of Q3GA (10 and 25 µM), closer to physiological values. The inhibitory effect of Q3GA was significant at 60 min and at 120 min for 25 and 10 µM, respectively. Protocatechuic acid (1 µM to 1 mM) had no relaxant effect in the aorta or mesenteric arteries (not shown). Figure 7 shows that the vasorelaxant effect of quercetin in a rat aorta was reversible upon washing with flavonoid-free solution. The relaxant effect of quercetin was unaffected by saccharolactone (not shown).

3.5 In vivo effects

Conscious rats had a mean arterial blood pressure of 123 ± 6 mm Hg. We administered an intravenous dose of 1 mg/kg Q3GA, which is expected to result in an immediate plasma concentration of ~25 µM, assuming 20 mL of plasma in 250 g of rat, which should then decay due to distribution, excretion and metabolism. This concentration is comparable with those achieved at 1 h after the oral doses of 10–50 mg/kg [25]. Q3GA induced a progressive and long-lasting decrease in blood pressure, which was significant at ≥60 min and reached a plateau at >100 min while the

![Figure 3. Metabolism of Q3GA at the perfused mesenteric bed. (A) HPLC chromatograms recorded at 370 nm of samples taken from the recirculated buffer at 10, 60, 180 and 360 min after the addition of Q3GA (100 µM). (B) Decay of Q3GA was accompanied by a progressive increase of quercetin in the perfusate. (C) The decay of Q3GA and the increase of quercetin in the perfusate was prevented by the presence of the β-glucuronidase inhibitor saccharolactone (300 µM). The results are expressed as mean ± SEM of three experiments.](image-url)
vehicle (saline) had no effect (Fig. 8A). Q3GA had no effect on heart rate compared with vehicle.

4 Discussion

The validity of a large number of studies analyzing the in vitro effects of quercetin and other flavonoids that are not present as free forms in plasma has been put into question. Some previous studies have shown that quercetin glucuronides can be deconjugated in vitro in cultured macrophages [24] and in homogenates from human liver and small intestine [26]. Despite quercetin being undetectable as a free form in the plasma of supplemented pigs, it can be found in relatively high concentrations in several tissues [27]. Herein, we have demonstrated that (i) Q3GA can be deconjugated enzymatically in a perfused vascular bed releasing free quercetin, which accumulates in the perfusing fluid and within the tissue; (ii) Q3GA is more stable than free quercetin in the vascular bed; (iii) Q3GA exerts inhibitory effects on vascular contraction in vitro when incubated for long time periods via the release of free quercetin; and (iv) quercetin-3-glucuronide exerts a progressive and long-lasting blood pressure lowering effect in vivo. Taken together, these results suggest that the circulating glucuronides in plasma behave as quercetin carriers and that the aglycone released in the target organs seems to be the final effector.

We first analyzed the metabolism of quercetin in the isolated perfused vascular bed. Quercetin disappeared rapidly from the recirculating buffer; within the time required for full mixing in the circuit more than half quercetin was lost from the fluid. Part of this can be attributed to the uptake by the tissue. However, the simultaneous appearance of protocatechuic acid indicates that metabolism accounts for most of the quercetin concentration decay. This elimination appears to be due to tissue-mediated oxidative degradation involving peroxidation and subsequent opening of the C-ring leading to the formation of the carboxylic acid [28]. Protocatechuic acid due to its high polarity remained in the recirculating buffer and it was not detected in the tissue. Despite the rapid decay in the buffer, quercetin was present in the tissue after long-term incubation, suggesting that it accumulates in a compartment in...
Figure 5. Inhibitory effects of Q3GA and quercetin (100 μM) on the contractile responses to phenylephrine in isolated endothelium-intact (A–E) or endothelium-denuded (F) mesenteric resistance arteries after 30 min (A, D) or 180 min (B, C, E, F) in the absence (A, B) or in the presence of 300 μM saccharolactone (C), L-NAME (D, E). The results are expressed as mean±SEM of 4–8 experiments. *p<0.05 versus control.

Figure 6. Inhibitory effects of Q3GA (10 or 25 μM) on the contractile responses to phenylephrine in isolated mesenteric resistance arteries after 30, 60 and 120 min (A) or after 120 min in the presence of saccharolactone (B). The results are expressed as mean±SEM of 4–8 experiments. *p<0.05 versus control.
which it is partly protected from degradation. Quercetin was accompanied by smaller amounts of methylquercetin but there was no evidence of glucuronidated metabolites.

Q3GA was more stable in the recirculating buffer than quercetin. The slow decay of Q3GA was accompanied by a parallel increase in quercetin, suggesting that deconjugation is the primary metabolic pathway for Q3GA. This was supported by the strong inhibitory effect of the β-glucuronidase inhibitor on Q3GA metabolism. In contrast to this in vitro model in which free quercetin slowly accumulates in the recirculating fluid, free quercetin in plasma is almost absent in in vivo experiments, presumably because it is rapidly re-glucuronidated in the liver [12, 13]. In addition, quercetin accumulated in the tissue and this was prevented by the β-glucuronidase inhibitor. Moreover, the concentrations of quercetin aglycone in the tissue continued to increase from 3 to 6 h after the addition of Q3GA while they decreased during this time interval when the aglycone was added. An interesting and intriguing finding of the present study is the fact that quercetin derived from the deconjugation of Q3GA was not further metabolized into protocatechuic acid. All this data support that circulating Q3GA acts as a stable store of quercetin, which slowly releases free quercetin avoiding its rapid degradation.

The vasorelaxant effects of quercetin and related metabolites have been widely assessed in vitro [6, 7]. Our previous results also showed that quercetin conjugated metabolites (Q3GA, quercetin-3'-O-sulfate or isorhamnetin-3'-O-glucuronide) have no direct vasorelaxant effect in isolated rat aorta [18] or in mesenteric arteries (unpublished) in either endothelium-intact or denuded arterial rings. In the present study, Q3GA when incubated for 30 min was also without effect. However, long-term incubation induced a progressive inhibitory effect on vascular contraction in a concentration- and time-dependent manner and these effects were independent of endothelium and nitric oxide. These results suggest that deconjugation is required for the biological effect. In fact, the β-glucuronidase inhibitor prevented the effect of Q3GA. Thus, we provide the first evidence correlating vascular deconjugation with biological activity. An important issue in order to correlate the concentrations of quercetin with its biological effect is whether the vasodilator effects of quercetin are reversible or not. Despite a large number of studies having shown the in vitro vasodilator effect of quercetin, to our knowledge none of them have addressed its reversibility after the washout. Herein, we...
show that when quercetin is removed, the contractile effect is almost fully recovered within 60 min.

We also addressed the in vivo vasodilator effects of Q3GA. The glucuronide administered intravenously, as it is found after oral administration of quercetin, induced a decrease in arterial blood pressure. To our knowledge, this is the first demonstration that Q3GA exerts effects in vivo. The slow onset and progressive blood pressure lowering effect is in agreement with the in vitro data and it is also consistent with the view that metabolism is required. Recently, an interesting hypothesis has been raised proposing that polyphenols are metabolized by the resident microbiota in the colon and the metabolites entering the systemic circulation may be responsible for the in vivo effects [29]. Our data show, however, that the effect of the flavonoid quercetin when given orally can be explained, at least in part, by the glucuronidated metabolite produced within the intestine and liver. Both mechanisms are not mutually exclusive and may, therefore, contribute to the biological effects associated to the intake of dietary flavonoids.

In conclusion, Q3GA can be deconjugated in the vascular bed, it can exert inhibitory effects on vascular contraction in the long term due to the release of the active aglycone and it also induces a long-lasting blood pressure lowering effect. We propose that quercetin, and possibly other related flavonoids, given orally is rapidly metabolized in the intestine and liver into glucuronidated derivatives which act as carriers of quercetin and deliver the free aglycone in situ by deconjugation.

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5 References


