REVIEW

Do polyphenols enter the brain and does it matter? Some theoretical and practical considerations

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Abstract Although several epidemiological and intervention studies suggest that polyphenols (PPs) and PP-rich foods may improve memory and cognition in animals and humans, PPs' mode of action is only poorly understood. To help distinguish between the different modes of action that have been proposed for PPs, it is obviously important to know how much PPs can accumulate in the brain, if any at all. However, reliable data on PP uptake into the brain of animals are limited as many studies failed to report important control procedures during data acquisition. In this paper, we summarize published data on the penetration of PPs into animal brain and review some hypotheses to explain the biological basis of potentially health-beneficial effects of PPs to the brain. Finally, we highlight promising new approaches, especially those of a hormetic dose-response and gut microbiota-brain interaction, which may allow a better understanding of PPs' mode of action in animals and humans.

Keywords Antioxidants · Effective brain concentration · Gut microbiota · Hormesis · Metabolic signalling · Polyphenols · Plasma concentration · Residual blood · Vitamin C

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Introduction

Several epidemiological studies suggest that diets rich in polyphenols (PPs) beneficially affect human brain function (Commenges et al. 2000; Letenneur et al. 2007). Similarly, supplementing rodents and humans with isolated PPs (Macready et al. 2009; Maher et al. 2006) or PP-rich foods and plant extracts (e.g. tea, blueberries or pine bark extract) (Andres-Lacueva et al. 2005; Francis et al. 2006; Macready et al. 2009; Nurk et al. 2009; Ryan et al. 2008) may improve memory and cognition. Numerous mechanisms, such as free radical scavenging, metal chelation and the modulation of enzyme activities, have been proposed for explaining a positive impact of PPs on the brain (Schaffer et al. 2006; Spencer 2008, 2009). However, the existence of direct antioxidant or other significant systemic effects of PPs, especially in the brain, are often met with scepticism, mainly due to the relatively poor intestinal uptake of PPs, their substantial biotransformation (so that blood and tissue concentrations of unaltered PPs are very low) and rapid excretion (Halliwell et al. 2005; Halliwell 2007a, b; Hollman et al. 2011; Hu 2007; Lotito and Frei 2006; Zini et al. 2006).

From first principles, PPs might alter brain function at three locations: (1) outside the CNS (for instance by improving cerebral blood flow or by modulating signalling pathways from peripheral organs to the brain), (2) at the blood–brain barrier (BBB, e.g. by altering multi-drug-resistant protein-dependent influx and efflux mechanisms of various biomolecules) and (3) inside the CNS (e.g. by directly modifying the activity of neurons and glial cells) (Ghosh and Scheepens 2009; Spencer 2007; Youdim et al. 2004). To help distinguish between these different modes of action, it is obviously important to know how much PPs can accumulate in the brain, if any at all. However, as many studies failed to report important control procedures,

reliable data on PP uptake into the brain of animals are limited. For obtaining meaningful information on this question, data ideally need to be collected either in exsanguinated and perfused animals (or tissues) or, alternatively, corrected for residual blood in the brain (Youdim et al. 2004). The importance of accurate in vivo measurements of brain drug exposure is highlighted in a recent study conducted in rats by Friden et al. (2010) who developed a mathematical model correcting drug brain concentrations for residual blood. After applying their model, the authors noted that concentrations of the drugs indomethacin and moxalactam in rat brain were significantly influenced by the amount of drug present in the residual blood.

In this paper, we first discuss published data on the penetration of PPs into animal brain. In cases where the PP-supplemented animals have neither been perfused nor residual blood in the brain has been corrected for as potential confounder, a correction of the reported PP brain concentrations has been attempted based on the mathematical model published by Friden et al. (2010). The second part of the current article summarizes some of the prevailing hypotheses for explaining the biological basis of potentially health-beneficial effects of PPs to the brain. Finally, we highlight promising new approaches that may allow for better understanding PPs' mode of action in animals and humans.

Concentration of polyphenols in brain and the effect of mathematical correction

Since the mid-1990s, the number of articles published on PPs has increased exponentially. However, despite the tremendous interest in PP research, only a small fraction of all studies addressed the important question of PP uptake and bioavailability (Fig. 1). Unsurprisingly, our knowledge regarding PP absorption, metabolism, tissue distribution, intracellular accumulation and excretion is insufficient.

So far, PP brain bioavailability has mainly been studied in rodents although at least one study was conducted in higher organisms, i.e. pigs (Tables 1 and 2). Exsanguinated and perfused animals are the gold standard for determining the amount of nutrient or drug that penetrated into the brain. Data from studies following this approach indicate that PPs usually accumulate at levels below 1 nmol/g tissue (Section 1 of Table 2). Similar findings result from studies where the brain PP concentration has been corrected for residual blood (Section 2 of Table 2). Furthermore, Janle et al. (2010) used accelerator mass spectrometry for detecting small amounts of labelled PPs in brain of perfused rats. Apart from this, a substantial number of articles reported brain PP uptake and concentrations without
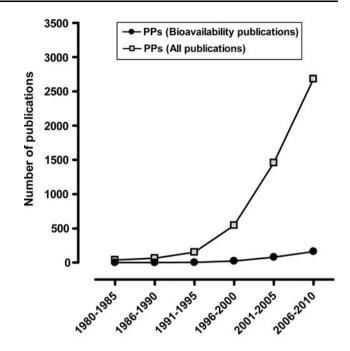

Fig. 1 Number of hits found for the search term 'polyphenols' or 'polyphenols AND bioavailability' in PubMed. The search field tag was limited to 'Title/Abstract'

considering residual blood as a potential confounder (Chang et al. 2000; Datla et al. 2001; Huebbe et al. 2010; Pan et al. 1999; Peng et al. 1998; Purkayastha et al. 2009).

In order to assess the magnitude of residual blood as a confounder in the quantification of brain PP concentrations, we applied a recently published mathematical correction model to one study, as an example (Friden et al. 2010). The limitation of this approach, however, is that studies only qualify for re-analysis when the mode of animal anaesthesia and killing ideally follow those published by Friden et al. (Table 3). In this case, the model can also be applied to other rodents, for example, mice (M. Friden, personal communication). The latter proposition is supported by a previous study reporting similar residual blood content (in per cent) for various rat and mouse organs (Schumann et al. 2007). Unfortunately, none of the studies on brain PP penetration available to us for evaluation strictly adhered to the above-mentioned criteria for re-analysis due to differences in the method of euthanasia and tissue sampling. However, as also mentioned by Friden et al. (2010), exsanguination by severing the heart seemed to result in *less* residual blood in rat brain compared to brain obtained from decapitated animals. Based on this notion, applying the correction model to studies where *more* residual blood in the brain samples will likely occur (as a result of the sampling procedure) can be considered conservative and will in most cases presumably still overestimate the amount of PP in the brain sample. Despite the above-mentioned

Table 1 Methodological parameters of studies assessing PPs concentrations in animal brain (inclusion criteria were either the usage of exsanguinated and perfused animals or the correction for residual blood by other means)

No.	PPs	Species	Route	Dosage	Duration	Sampling	Anaesthesia	Killing and tissue collection	References
Section I: studies in exsanguinated and perfused animals									
1	Epicatechin	Rat	Oral	100 mg/kg BW	1 day	2 h after PP intake	Phenobarbitone	Plasma: Decapitation — Brain: Perfusion	Abd El Mohsen et al. (2002)
2	Pelargonidin	Rat	Oral	50 mg/kg BW	1 day	2 h and 18 h after PP intake	Pentobarbitone	Perfusion	El Mohsen et al. (2006)
3	Grape seed extract	Rat	Oral	300 mg/kg BW (twice daily)	3 days	4 h after last PP intake	Isoflurane	Cervical dislocation and heart puncture followed by perfusion	Prasain et al. (2009)
4	Grape seed extract	Rat	Oral	Dose-escalating design. Days 1–2: 50 mg/kg BW. Days 3–4: 100 mg/kg BW. Days 5–10: 150 mg/kg BW	10 days	8 h after last administration	–	Plasma: Collected from jugular vein (catheter). Brain: Perfusion	Ferruzzi et al. (2009)
5	Blackberry extract	Rat	Oral	15 g/kg diet (with 14.8 mmol anthocyanins/kg diet)	15 days	3 h after last meal	Pentobarbital	Blood: All blood drawn from abdominal aorta. Brain: removed from bloodless animals	Talavera et al. (2005)
6	Epigallo catechin-3-gallate	Rat	Oral	500 mg/kg BW	1 day	1 h after administration	Ether	Blood: Collected from abdominal artery. Brain: Perfusion	Nakagawa and Miyazawa (1997)
7	Quercetin	Rat	Oral	1% w/w	1 month	No details given	Pentobarbital	Blood: –. Brain: Perfusion	Ishisaka et al. (2011)
Section II: studies correcting for residual blood									
8	Quercetin	Rat	Oral	0.1% in diet	11 weeks	Morning w/out overnight fasting	Isoflurane	Full bleeding from aorta	de Boer et al. (2005)
9	Quercetin	Pig	Oral	500 mg/kg BW	3 days	Fasting for 8 h	No details given	No details given	

BW body weight

limitations, we suggest that our approach highlights the often underappreciated problem of confounded levels of PPs in brain tissue reported in the scientific literature.

In the study selected for re-assessment, female mice (6–7 weeks old) were fed a PP-poor, semi-synthetic diet supplemented with quercetin (2 g/kg diet) for 6 weeks (Huebbe et al. 2010). The brain concentrations of quercetin and its metabolite, isorhamnetin, at baseline and at the end of the intervention for both control and supplemented animals are depicted in Fig. 2. The results of the mathematical correction model indicate that the actual amounts of brain quercetin and isorhamnetin in supplemented mice are about 8 and 27% lower, respectively, whereas values for control animals remained unchanged. Although only of moderate magnitude, the corrected values for brain PPs, especially of isorhamnetin, suggest that residual blood might confound supplementation studies aiming to quantify the enrichment of PPs in brain beyond baseline data. Somewhat surprising are the high baseline levels of quercetin in the brain of control animals

Table 2 PPs concentrations in plasma and animal brain obtained from studies using either exsanguinated and perfused animals or correcting for residual blood by other means

No.	PP measured	Plasma conc.	Correction achieved by	Brain conc. corrected	References
Section I: studies in exsanguinated and perfused animals					
1	Epicatechin metabolites (total)	66 uM	Perfusion	0.4 nmol/g tissue (estimated)	Abd El Mohsen et al. (2002)
2	Pelargonidin metabolites (total)	2 h: ∼1.5 uM	Perfusion	2 h: 0.16 nmol/ tissue [43 ng/g]	El Mohsen et al. (2006)
		18 h: ∼0.65 uM		18 h: <LOD	
3	(+)-Catechin	<LOD	Perfusion	53 ng/g tissue	Prasain et al. (2009)
4	Catechin	1.98 ug/ml	Perfusion	0.57 ng/g tissue	Ferruzzi et al. (2009)
	Epicatechin	3.86 ug/ml		0.29 ng/g tissue	
5	Cyanidin-3-glucoside	0.15 uM	Blood-less animals used; no explicit information on brain perfusion	0.21 nmol/g tissue	Talavera et al. (2005)
6	Epigallocatechin-3-gallate	12.3 uM	Perfusion	0.5 nmol/g tissue	Nakagawa and Miyazawa (1997)
7	Quercetin	No details given	Perfusion	40.1 pmol/g tissue	Ishisaka et al. (2011)
Section II: studies correcting for residual blood					
8	Quercetin	7.7 umol/l	Hb method	<LOD	de Boer et al. (2005)
	Isorhamnetin	15.7 umol/l		0.19 nmol/g tissue	
	Tamarixetin	<LOD		0.14 nmol/g tissue	
9	Quercetin	1.1 umol/l	Hb methods	0.22 nmol/g tissue	
	Isorhamnetin	0.15 umol/l		<LOD	
	Tamarixetin	<LOD		<LOD	

LOD limit of detection

Table 3 Anaesthesia and tissue collection procedure prior analysis of brain drug concentrations and their mathematical correction as published in Friden et al. (2010)

Step	Procedure
1	Anaesthesia with isoflurane
2	Collection of blood sample from abdominal aorta (2 mL) for analysis
3	Exsanguination by severing the heart
4	Removal of brain, taking of coronal section for analysis

despite the low quercetin concentrations (0.12 μM) in blood. The authors provided two possible explanations for this observation: (1) the transfer of quercetin from the mothers to their offspring during the intrauterine development and (2) the uptake of quercetin (and its subsequent accumulation in the brain) from a standard feed (Huebbe et al. 2010). Although it is still difficult to say from current data whether some PPs not only accumulate but also persist (as the quercetin data for the control animals suggest) in specific target organs for longer periods of time, data published for other bioactive compounds, in particular the naturally occurring amino acid ergothioneine, are consistent with this notion (Cheah and Halliwell 2011).

Nonetheless, results from the aforementioned mouse study (Huebbe et al. 2010) in combination with those reports listed in Table 2 provide reasonable evidence that PPs do enter the brain at measurable levels. An additional important parameter affecting the correction for residual blood and subsequently the uptake of drug into brain is protein binding (Friden et al. 2010). For example, Diniz et al. (2008) observed significant, structure-dependent differences in the binding behaviours of PPs to plasma proteins, ranging from more than 90% human serum albumin (HSA) binding affinity for PPs such as apigenin and quercetin to below 10% as, e.g., in the case of epicatechin. Noteworthy, plasma fatty acids allosterically inhibit PP binding to HSA (Bolli et al. 2010), suggesting that dietary factors might modulate PP plasma, and subsequently, tissue distribution. The accuracy of PP quantification in brain, of course, also significantly depends on other parameters, such as PP extraction efficiency from the tissue as well as on the applied analytical method (Wilkinson et al. 2002).

Does it matter that polyphenols can enter the brain?

Classically, PPs are considered as potent antioxidants due to their ability to directly scavenge free radicals and other reactive species (RS, for details see Halliwell 2006) in vitro
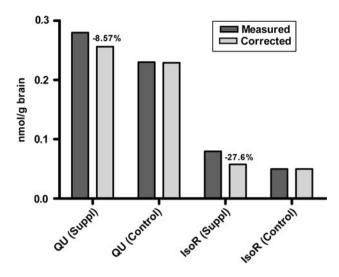
Fig. 2 Effect of mathematical correction for residual blood on the published concentrations of quercetin (OU) and isorhamnetin (IsoR) in the brain of quercetin-supplemented mice (Huebbe et al. 2010). For details see text

(Pannala et al. 1997; Russo et al. 2000; Visioli et al. 1998) and perhaps sometimes also in vivo. Given the brain's vulnerability to oxidative and nitrosative stress, the sufficient supply of the CNS with antioxidants is of prime importance (Halliwell 2006; Reiter 1995).

In the following, we compare the ability of PPs to act as brain antioxidants with ascorbic acid (AA, vitamin C) one of the most abundant low-molecular-mass antioxidants in the mammalian brain (Rice 2000). AA levels of about 2,000 nmol/g tissue have been measured, for instance, in the brain of perfused, male Wistar rats (Sun et al. 1999). Some caution has to be taken when conducting vitamin C studies in rats and mice (both rodent species not only possess a much higher neuron density per mm^3 than humans—and consequently greater AA content per g brain tissue—but are also able to synthesize their own vitamin C, unlike humans who depend on a dietary AA supply). Nevertheless, rat brain AA levels are in a similar range to those reported for guinea pigs, which need vitamin C from the diet (about 1,500 nmol/g tissue; perfused animals Lykkesfeldt et al. 2007), but are (as expected) higher than in humans (about 600–900 nmol/g tissue) (Rice 2000; Terpstra et al. 2011). Compared to PPs (for details see Table 2), AA brain concentrations of perfused laboratory rodents are thus about 3,000–4,000 times higher, making it rather unlikely that PPs, even when considering their several fold higher in vitro antioxidant activity (Rice-Evans et al. 1995; Schaffer et al. 2004), exert appreciable direct RS-scavenging effects in the mammalian brain, unless they act in different compartments, e.g. lipids, depending on their solubility in lipophilic and hydrophilic environments.

Furthermore, the question of whether compounds such as AA and PPs are active within the CNS also depends on their compartmentalization between the cerebrospinal fluid (CSF), extracellular fluid (ECF) and the different types of brain cells. Concentrations of AA are highest in neurons (~ 10 mM), followed by glial cells (~ 1 mM), CSF (~ 500 μM) and ECF (200–400 μM) (Rice 2000). Our knowledge of PP compartmentalization within the CNS, on the other hand, is rather scarce. Data from in vitro studies, however, might serve as a first approximation. First of all, there is now good evidence from cell culture experiments that PPs are able to enter at least some cell types (Ernst et al. 2010; Watjen et al. 2005), and in a few studies, actual PP uptake has been quantified (Table 4). Assuming an average cell volume of 22×10^{-13} l [=22 picolitres, based on cell volume data for HepG2 cells of 12.1×10^{-13} l, PC12 cells of 20.5×10^{-13} l and cardiac myocytes of 33.4×10^{-13} l (Atkins et al. 1991; Leung et al. 1994; Wehner et al. 2002)], an estimated quercetin uptake of 20 nmol/10^6 cells would result in an intracellular quercetin concentration of 9 mM. This, however, would require the extracellular presence of PPs at un-physiological concentrations of a few hundred micromolar (Table 4). As there is currently no evidence that CSF and ECF concentrations of PPs exceed 1–5 micromolar (at best), it is thus highly unlikely that intracellular PP concentrations in neurons and glial cells will exceed the very low micromolar to nanomolar range. This, clearly, is not sufficient for exerting any appreciable direct antioxidant effect (compared, e.g., to vitamin C and glutathione)—but might still be high enough to modulate other cellular parameters in the CNS (see below).

Direct antioxidant effects of PPs are thus not very likely in the brain in vivo, nor are there any literature data we are aware of measuring accurate biomarkers of oxidative damage that show that PPs have direct antioxidant effects in the brain. We ought to consider the absence of evidence as evidence of absence for direct RS-scavenging activities of PPs in animals and humans, especially as PPs levels in vivo are likely too low to matter in the face of endogenous antioxidants (Halliwell and Gutteridge 2007).

How, then, can we explain the several studies reporting positive effects for PPs on brain function? One research field attracting more and more attention is the modulation of monoaminergic and GABA neurotransmission by PPs. The treatment of rats with PP-rich *Ginkgo biloba* extract for 14 days, for example, resulted in significantly increased extracellular levels of dopamine and noradrenaline (but not of serotonin) in the animals' prefrontal cortex (Yoshitake et al. 2010). Of the three main *Ginkgo biloba* extract constituents, the PP (flavonoid) fraction caused a significant (and most pronounced) increase in brain dopamine levels, whereas ginkgolides had only a moderate and

Table 4 Cellular uptake of PPs reported for different cell lines

PP	Test conc. (μM)	Incubation time	Cell line	Intracellular conc.	Study
Apigenin	50	2 h	Caco-2	∼1.2 nmol/mg protein	Yokomizo and Moriwaki (2006)[a]
Kaempferol				∼1.8 nmol/mg protein	
Luteolin				∼1.3 nmol/mg protein	
Quercetin				∼0.9 nmol/mg protein	
Myricetin				ND	
Myricetrin				ND	
Rutin				ND	
Isoquercitrin				ND	
Quercetin	500	1 h	H4IIE	33.4 nmol/10^6 cells	Watjen et al. (2005)
Fisetin				12.67 nmol/10^6 cells	
Myricetin				0.22 nmol/10^6 cells	
Morin				2.35 nmol/10^6 cells	
Taxifolin				0.2 nmol/10^6 cells	
Rutin				0	
Catechin				0	
EC	50	1 h	Caco-2	0	Vaidyanathan and Walle (2003)[a]
(+)-Catechin				∼150 pmol/mg protein	
ECG				∼3,000 pmol/mg protein	
EGCG				∼2,400 pmol/mg protein	
Quercetin	5	30 min	HepG2	∼900 pmol/mg protein	Boulton et al. (1999)[a]

ND not detected

PP polyphenols

[a] Data were estimated from graphs

bilobalides no effect (Yoshitake et al. 2010). The observed effects appear not to depend on the activity of monoamine oxidases (MAO-A and MAO-B) as these were unchanged in mice chronically treated with the extract (Fehske et al. 2009). The low concentration of PPs in brain (Table 2) compared to the K_i values, for instance, of quercetin for MAO-A of 7.26 μM and for MAO-B of 7.95 μM (Dixon Clarke and Ramsay 2011) suggests that other parameters, such as neurotransmitter re-uptake mechanisms, might be involved in the modulation of monoaminergic neurotransmission by PPs (Fehske et al. 2009; Ofir et al. 2003). Mood and behavioural disorders often arise from a dysfunctional neurotransmission and thus might benefit from drug-induced alterations in the amount of available neurotransmitters within the CNS (Racagni and Popoli 2010). Neurotransmitter re-uptake inhibition in synaptosomal preparations has been reported for some PPs and PP-rich plant extract fractions (e.g. resveratrol, catechin or *Ginkgo* flavonoids) but not others (e.g. kaempferol) (Muller et al. 1998; Rocha et al. 2007; Yanez et al. 2006). Similarly, a plethora of in vitro data indicates that PPs act as modulators of the GABA$_A$-benzodiazepine receptor. Whereas the K_i values for the affinity of many PPs to the receptor is in the one-digit to two-digit micromolar range, some PPs are effective at lower (and maybe physiologically achievable) concentrations,

such as amentoflavone with reported K_i values of 6–56 nM (Jager and Saaby 2011). Much more work, however, needs to be done in order to understand whether the same PP actions on GABA$_A$ receptors occur in vivo and, even more challenging, by what mechanism (Hanrahan et al. 2011; Jager and Saaby 2011).

Based on today's knowledge, other promising explanations of the possible brain effects of PPs are also indirect in nature: (1) the activation of a hormetic dose-response and (2) effects on peripheral systems of the body, which in turn influence CNS functioning.

Hormesis describes a process in which exposure to a low dose of an agent that is toxic at higher doses induces a beneficial effect on the cell or organism (Mattson and Cheng 2006). Whereas most studies describing hormetic effects for PPs have been performed in cell culture or the nematode *C. elegans* (Ali and Rattan 2006; Gruber et al. 2007; Pietsch et al. 2011; Wagner et al. 2011), recently, the first direct evidence for hormesis induction in vivo has been reported in mammals. Pretreatment of mice with the PP epicatechin significantly reduced the negative impact of stroke induction in wild-type but not Nrf2 knock-out animals (Shah et al. 2010). As the transcription factor Nrf2 is one of the key regulators responsible for the induction of antioxidant and cell protective genes, this study suggests

that PPs might indeed operate by hormesis activation. One caveat affecting the evaluation of hormetic phenomena, however, needs to be considered based on ontogenetic studies, i.e. that a subject's developmental stage might influence the magnitude of an observed hormetic response. For example, the U-shaped effects of acute ethanol exposure on overall social activity of rats are not only influenced by the measuring time post-exposure but are also strongly age-dependent (Spear and Varlinskaya 2005). Similarly, changes in the penetration efficiency of substances due to the disruption of the blood–brain barrier, for example in stroke (Cipolla et al. 2004), might shift the dose-response away from reference values, posing either the risk of unexpected side effects or the possibility for an improved therapeutic outcome. Some authors also noted the lack of a precise definition of hormesis and furthermore pointed out that the evaluation of a hormetic response in terms of possible health effects must be carefully studied as compounds, even at low dose, might exert significant beneficial or detrimental effects on physiological and cellular mechanisms, which are often non-linear and chaotic in nature, such as coronary circulation, neuronal signalling or calcium oscillation (Chirumbolo 2011; Clay and Shrier 1999; Haberichter et al. 2001; Trzeciakowski and Chilian 2008). The perturbing impact of PPs at concentrations as low as 1 µM on cellular signalling pathways and metabolic processes has been demonstrated, for example, for PP-dependent effects on mitochondrial calcium uptake and on the activity of protein kinase C (Kalfon et al. 2007; Montero et al. 2004). Note that there is currently a trend of moving away from studying PP parent compounds and towards the assessment of biological activities exerted by PP metabolites and degradation products. Several extensive reviews regarding the consequences of PPs and their metabolites on cellular mechanisms are available (Lau et al. 2005; Manach et al. 2004; Spencer et al. 2004, 2007; Visioli et al. 2011), although the overall picture remains somewhat diffuse given the impressive number of signalling pathways shown to be affected. Whereas little is known about the in vivo effects of PP metabolites and degradation products on the brain, evidence from some studies indicates that these compounds might also enter the CNS, although usually at a very low level (Abd El Mohsen et al. 2002; Ferruzzi et al. 2009; Huebbe et al. 2010).

However, many activities of PPs have, so far, only been demonstrated in cell culture studies, which are prone to artefacts (Halliwell 2003). Upon exposure to standard cell culture media (e.g. DMEM, MEM or RPMI), many PPs become degraded and, at the same time, initiate the production of hydrogen peroxide in the one-digit to three-digit micromolar range (Long et al. 2010; Schaffer and Halliwell 2011). Common medium supplements (such as pyruvate) or excreted cellular metabolites (for instance

α-ketoglutarate) effectively scavenge PP-derived hydrogen peroxide and thus become depleted, which can affect results where pyruvate or α-ketoglutarate are important growth factors to the cells being cultured (Long and Halliwell 2009, 2011). Hence, careful thought is essential when elucidating the in vivo mode of PP action and subsequently their possible areas of preventive or therapeutic application in humans.

Furthermore, the regulation of brain integrity and function must not be seen in isolation but as strongly dependent on feedback information (in the form of hormones, nutrients, metabolites and, of course, sensory neuron signalling) of the body periphery. In addition, mainly physico-mechanical parameters, such as the amount of blood supplied to the brain, are important factors to consider when assessing CNS effects of patho-physiological events and preventive/therapeutic interventions (e.g. drugs and diet). Endothelial dysfunction, for example, is associated with reduced cerebral perfusion and the occurrence of dementia (Ghosh and Scheepens 2009). Reasonable evidence exists that PPs from cocoa (Francis et al. 2006; Heiss et al. 2007; Heiss et al. 2010) and other dietary sources, such as tea (Grassi et al. 2009) and grapes (Lekakis et al. 2005), increase blood flow in humans, thus possibly helping to provide the brain with greater amounts of oxygen and glucose. Negative studies, however, have also been published on this topic (Auclair et al. 2010; van Mierlo et al. 2010). A recurrent observation in many studies assessing the effect of bioactive compounds (PPs, phytochemicals and plant extracts) is the strong impact of age and health status on the study outcome. Several clinical trials indicate that young- to middle-aged healthy human subjects often do not benefit from the intake of bioactive compounds when applied in the form of antioxidant supplements or antioxidant-enriched foods (Boots et al. 2008; Canter and Ernst 2007; Kelly et al. 2008; Lee et al. 2009). Also, older humans suffering from advanced stages of chronic diseases (such as Alzheimer's disease) reveal negligible or zero therapeutic effects when the patients are treated with PPs or other phytochemicals (Daviglus et al. 2010; Lloret et al. 2009; Quinn et al. 2010). Thus, clearly more work is needed in order to identify the optimal time frame for preventive and therapeutic interventions in humans, probably not too young and not when disease has progressed to an advanced stage.

Another example highlighting the impact that peripheral organs can exert on brain (mal)function is metabolic signalling by the gastro-intestinal tract (GIT). Compared to blood, dietary PPs can be present in high amounts in the GIT and could even exert direct antioxidant effects there, e.g. in the stomach (Halliwell et al. 2000, 2005; Kanner and Lapidot 2001). Some PPs also reach the colon (Jenner et al. 2005; van Duynhoven et al. 2011). In the past 5–10 years, exciting new information regarding health implications of the

brain-gut-enteric microbiota axis has emerged (Rhee et al. 2009). Whereas some aspects of this bidirectional interaction are well established, for instance the effect of mucosal inflammation on pain reception, effects of gut microbiota on other CNS-regulated phenomena such as mood changes or anxious behaviour have only recently been described (Forsythe et al. 2010; Rhee et al. 2009). A new study by Heijtz et al. (2011) emphasizes the importance of gut microbiota for brain development and behaviour. When comparing specific pathogen-free with germ-free mice, the authors found significant differences in motor control and anxiety-like behaviour between the two mouse groups, possibly indicating that evolution might have driven the link between gut microbiota and brain development. As PPs strongly affect both composition and metabolism of the intestinal microbiota, it is possible that this interaction might exert effects not only on the GIT but also indirectly on the brain, especially when considering that luminal microorganisms (about 10^{11} bacterial cells per gram colon content) represent 100 times the total genetic material contained in a human body, thus allowing for a stunning production of a wide range of metabolites (Forsythe et al. 2010; Rhee et al. 2009). Most of the biological activities that these microbial metabolites exert on the human body, and especially the brain, are currently unknown, but they might soon be revolutionizing how we look at human health and disease.

In conclusion, what does the scientific community need to do with respect to PP research? We propose two adjustments: (1) the development of more sophisticated analytical methods to establish levels of PPs and their metabolites to confirm the view that direct effects on brain cells and tissue are likely or unlikely and (2) a significant spike in non-reductionist research efforts for elucidating bi- and even multi-directional inter-organ actions and reactions, especially between peripheral organs and the brain, which are too often studied in isolation. Furthermore, in order to master the likely overwhelming amount of data associated with such complex research agendas, experimental research should ideally go hand-in-hand with systems biology (Assmus et al. 2006; Desiere 2004; Lemberger 2007). Only then, we predict, will the biomedical research community be able to significantly advance our understanding of the effects of PPs as external and internal determinants of human health and disease.

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