Commentary

Relationship between Mechanisms, Bioavailibility, and Preclinical Chemopreventive Efficacy of Resveratrol: A Conundrum

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Experience has taught us that the rational clinical development of novel putative cancer chemopreventive agents needs to be based on robust preclinical information. Such information should relate to the mechanism of action, pharmacodynamics, and pharmacokinetics of the agent under study. Deficiencies in knowledge of any of these areas confound the understanding of the reasons for failure, when in a costly intervention trial, an agent is found to lack activity. The ramifications of such deficiencies are exemplified by the discussions engendered by the β-carotene intervention trials in the early 1990s (1). In this commentary, we scrutinize recent preclinical information on the promising and novel diet-derived putative cancer chemopreventive agent resveratrol (3,5,4′-trihydroxy-*trans*-stilbene), with the aim of preparing the ground for its clinical evaluation. Resveratrol is a phytoalexin generated in response to environmental stress or pathogenic attack in grapes, mulberries, cranberries, peanuts, and plants of the *Cassia quinquangulata* family.

Activity of Resveratrol in Cells and Biosystems *in Vitro*. In 1996, Jang *et al.* (2) published a paper in which the ability of resveratrol to inhibit diverse cellular events associated with the three major stages of carcinogenesis (initiation, promotion, and progression) was described. This seminal paper undoubtedly fired the imagination of the cancer chemoprevention research community. During the 6 years since its publication, ~100 reports have appeared in the literature in which cellular and biochemical mechanisms of this agent have been elucidated, and their potential role in the suggested cancer chemopreventive activity of this agent has been discussed. These mechanistic studies have been comprehensively summarized in several reviews (3–7), and Table 1 illustrates some of the mechanistic properties of resveratrol *in vitro*, but the list is certainly not exhaustive. Collectively, the investigations of biochemical and cellular mechanisms of activity of resveratrol *in vitro* (Table 1) suggest that it engenders changes relevant to cancer chemoprevention at the level of the cell or the isolated subcellular target system, when used at concentrations between 10 and 100 μM. Only on very few occasions have concentrations <10 μM been shown to elicit bioactivity, *e.g.*, IC_{50}s for cellular growth inhibition by resveratrol tend to span the 5–10 μM range (3); it inhibited recombinant cytochrome P450 CYP1B1 enzyme activity at 1 μM (8), and it exerted antiestrogenicity in cells at submicromolar concentrations (9).

There are two pivotal questions relating to the appropriateness of translating these *in vitro* results to animals and humans *in vivo*: (*a*) can 10^{-5}-10^{-4} M concentrations of resveratrol be achieved *in vivo* in the intact mammalian target organ in which malignancies are to be prevented; and (*b*) are doses of resveratrol, which have been shown to delay or prevent malignancies in rodent models, consistent with the attainment of such target organ levels? It is perhaps surprising that, to our knowledge, there has been no study on resveratrol published thus far probing the link between target organ levels, efficacy *in vivo*, and activity observed in cells *in vitro*.

Levels of Resveratrol and its Metabolites in Humans and Rodents. How much resveratrol can be recovered from the human or rodent organism after resveratrol consumption? The resveratrol content of wine is ~5 mg/liter. Assuming moderate wine consumption (250 ml in a 70-kg person), the intake of resveratrol with wine in humans is ~18 μg/kg/day. In a recent study in healthy volunteers, resveratrol was administered at a dose of 360 μg/kg either dissolved in grape juice, vegetable juice, or white wine, *i.e.*, at a dose which was 20 times that associated with "normal" wine intake (10). The authors used a very sensitive gas chromatography-mass spectrometry method and found plasma peak levels of 20 nM authentic resveratrol and 2 μM "total" resveratrol (*i.e.*, genuine resveratrol plus resveratrol generated by hydrolysis of its conjugates) 30 min after ingestion, irrespective of dietary matrix. Results from preclinical studies in rats, using exclusively high-performance liquid chromatography methods, suggest consistent attainment of plasma peak levels 5–10 min post-oral administration and a rapid plasma elimination half-life of 12–15 min. However, these studies differ as to the actual peak level values: doses of 2 mg/kg (11), 20 mg/kg (12), and 50 mg/kg resveratrol (13), each given via the *i.g.* route, generated peak values of 2, 1.2, and 6.6 μM, respectively. In the latter study, the peak level of resveratrol glucuronide was as high as 105 μM, and the authors present convincing evidence for extensive enterohepatic circulation (14). Using radiolabelled resveratrol administered by the oral route, an appreciable fraction, 50–75% of the dose, was absorbed in rats (14), and radioactivity could be recovered from the stomach, liver, kidney, intestine, bile, and urine in mice (15). Studies in mice, rats, and dogs suggest consistently that resveratrol is well absorbed and rapidly glucuronidated and sulfated both in the liver and intestinal epithelial cells (14–18). In investigations using a perfused rat small intestine model, ample uptake and metabolism of resveratrol occurred in the gut *ex vivo* (17, 19). Furthermore, resveratrol underwent glucuronidation and sulfation readily in liver cells and human and rodent liver and gut subcellular fractions (18, 20, 21). Taken together, all of these metabolism and pharmacokinetic investigations suggest convincingly that resveratrol is satisfactorily absorbed from the rodent gastrointestinal tract and efficiently

Received 6/27/03; accepted 7/1/03.
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Table 1 Mechanisms of resveratrol in cells *in vitro* related to cancer chemoprevention

Mechanism	Experimental system	"Efficacious" concentrations (μM)[a]	Reference
Inhibition of growth	Multiple cell lines	~5–10	5 (review)
Induction of apoptosis	Leukemia cells	32–100	34, 35
Induction of p-53-independent apoptosis	Colon tumor cells	100	36
Estrogen agonism	Mammary cells	10–25	9
Antiestrogenicity	Mammary cells	0.1–1	9
Inhibition of oxygen radical formation nitric oxide production	Macrophages	~30	37
Inhibition of cytochrome P450 enzymes: CYP1A1 CYP1B1, CYP3A4	Liver cells, microsomes, recombinant enzyme	1–20	8, 38, 39
Activation of p53	Mouse epidermal cells	20	40
Activation of c-jun kinase	Mouse epidermal cells	10–40	41
Decrease in COX-2 expression	Mammary epithelial cells	~5	42
Increase in p21/Cip1, cyclins D1, D2, E; decrease in cdks 2, 4, 6	Epidermoid carcinoma cells	~10	43
Increase in cyclins A, B1, and cdks 1 and 2	Colon tumor cells	30	44
Inhibition of protein kinase C activity	Gastric cells	50	45
Inhibition of protein kinase D activity	Fibroblasts	>100	46
Inhibition of NF κB[b] activation	Monocytes, macrophages	30	47
Inhibition of NF κB and AP-1 activation	Myeloid, lymphoid, epithelial cells	5	48

[a] Lowest concentrations at which reproducible changes have been observed, or IC_{50} or EC_{50}, if provided.
[b] NF κB, nuclear factor κB.

Table 2 Dose, chemopreventive efficacy, and putative peak plasma levels of resveratrol in preclinical animal models *in vivo*

Model[a]	Daily dose[b]	Route	Efficacy[c]	Putative peak plasma levels[d] (μM)	Reference
NMU-induced breast cancer in rat	100 mg/kg	Ig[e]	+	~14	22
	10 mg/kg	Ig	−	~1–2	
AOM-induced colon cancer in rat	200 μg/kg	Drinking water	+	~0.02	26
DMBA-induced breast cancer in rat	1 mg/kg	Diet	+	~0.1	28
NMBA-induced oesophageal cancer in rat	1 or 2 mg/kg	i.g. or i.p.	+	~0.1–1	27
$Apc^{Min+/+}$ mouse	15 mg/kg	Drinking water	+	~1–2	23

[a] AOM, azoxymethane; DMBA, 7,12-dimethylbenz(*a*)anthracene.
[b] Doses of resveratrol admixed to the diet or drinking water are approximate.
[c] +, efficacious; −, inefficacious.
[d] Peak levels are grossly approximated on the basis of extrapolation from pharmacokinetic data presented in Refs. 10–13.
[e] Ig, immunoglobin.

metabolized via conjugation in the liver and gut. Most importantly, peak plasma levels of unmetabolized resveratrol in the rat are well below 10 μM, even after a high oral dose of 50 mg/kg, and its elimination is rather rapid. In contrast, resveratrol conjugates seem to reach much higher plasma levels than the parent agent.

Cancer Chemopreventive Efficacy of Resveratrol in Rodents *in Vivo*. Which doses of resveratrol are required to delay or prevent malignancies in carcinogen-induced or transgenic rodent models of carcinogenesis? In Table 2, preclinical rodent models in which resveratrol has been tested are listed, and the doses administered are juxtaposed with putative peak plasma levels following these doses, with levels grossly extrapolated from the data presented in Refs. 10–13. In general, biologically effective doses of polyphenols, such as the flavonoids (exemplified by genistein and quercetin) and tea constituents (such as epigallocatechin gallate), administered daily over a long time period, have been in the range of 10–500 mg/kg, when given by *i.g.* intubation, or between 0.01 and 0.5%, when admixed with the diet or drinking water. These dietary concentrations translate into doses of ~15–750 mg/kg in the mouse and 10–500 mg/kg in the rat. Consistent with this generalization, resveratrol delayed NMU[2]-induced mammary tumors in rats significantly at daily doses of 100 mg/kg *i.g.*, whereas 10 mg/kg was ineffective (22). In the $Apc^{Min/+}$ mouse model, 0.01% resveratrol in the drinking water (constituting a dose of ~15 mg/kg/day) has been reported to reduce adenoma load by 70% (23). However, this result needs to be interpreted with utmost caution in light of two subsequent contradictory abstracts. They suggest that in the same murine model, dietary doses comparable with, or much higher than, those used by Schneider *et al.* (23) were completely ineffective (24) or, in the case of a dietary daily dose of 500 mg/kg for 14 days, reduced adenoma load by 50% but did so only in male mice and not at all in females (25).

There have recently been three intriguing publications which describe extraordinary *in vivo* potency of resveratrol in rat carcinogenesis models. These reports claim objective efficacy at much lower doses of resveratrol than those used in most studies of putative cancer chemopreventive polyphenols (Table

[2] The abbreviations used are: NMU, *N*-methyl-*N*-nitrosourea; NMBA, *N*-nitrosomethylbenzylamine; DMBA, 7,12-dimethylbenz(*a*)anthracene; COX, cyclooxygenase.

2). Firstly, Tessitore *et al.* (26) suggest that in the azoxymethane-induced rat colon carcinogenesis model, resveratrol dissolved in the drinking water at the extremely low dose of ~200 μg/kg/day decreased the number of colonic aberrant crypt foci by 40% and their multiplicity by 50%. This efficacy was accompanied by an increase in the expression of the proapoptotic protein Bax in the foci and attenuation of expression of the cell cycle inhibitory protein $p21^{Cip1}$ in normal colonic mucosa in these rats. The second of these studies reports that in rats which received NMBA to induce the formation of esophageal carcinoma, resveratrol at only 1 or 2 mg/kg either administered via the *i.g.* or *i.p.* route decreased tumor number and size (27), *e.g.*, doses of 1 mg/kg *i.p.* daily for 20 weeks, or 2 mg/kg *i.g.* daily for 16 weeks, decreased tumor multiplicity by 52 and 38%, respectively. These decreases were accompanied by attenuation of the NMBA-induced overexpression of the enzymes COX-1 and 2. Thirdly, Banerjee *et al.* (28) found that in the DMBA-induced mammary carcinogenesis rat model, as little as 10 ppm resveratrol in the diet, which translates into a dose of 1 mg/kg/day, decreased tumor incidence by 45% and tumor multiplicity by 55%. This efficacy of resveratrol was accompanied by a reduction in DMBA-induced elevation of expression of COX-2 and matrix metalloprotease 9 and of DMBA-mediated activation of the transcription factor nuclear factor κB.

The Resveratrol Conundrum and How to Resolve It. The remarkable message emanating from these three preclinical efficacy papers (26–28) is that exquisitely low daily doses of resveratrol (between 200 μg/kg and 2 mg/kg), which according to the pharmacokinetic results presented above give peak plasma concentrations of unmetabolized resveratrol of probably 20 nM up to, at the very most, 2 μM, and more likely considerably less, suffice to exert potent cancer chemopreventive efficacy and pharmacodynamic activity in three chemical-induced rat carcinogenesis models. These reports render resveratrol one of the most potent diet-derived chemopreventive dietary polyphenols ever described. In contrast, most mechanistic studies *in vitro* suggest that carcinogenesis-modulating effects of resveratrol require the sustained presence of 5–100 μM. This discrepancy is glaringly illustrated in the study by Banerjee *et al.* (28). On the one hand, the authors demonstrate impressive breast cancer chemopreventive efficacy *in vivo* of resveratrol at a dose of 1 mg/kg, which is unlikely to yield plasma peak levels >~1 μM (based on Refs. 11–13). On the other hand, they suggest in the same study that growth inhibition and nuclear factor κ B inactivation elicited by resveratrol in MCF-7 cells *in vitro*, at an extent comparable with that seen *in vivo*, requires resveratrol concentrations of 25–50 μM. The conundrum is summarized by the following three statements: (*a*) resveratrol at doses as low as 200 μg/kg to 2 mg/kg elicits chemopreventive efficacy in some rat models; (*b*) such efficacy is supposed to be mediated via mechanisms which *in vitro* are engaged by agent concentrations of ≥5–100 μM; and (*c*) in light of the avid biotransformation of resveratrol, its bioavailibility *in vivo* is likely to be grossly insufficient to furnish agent levels compatible with those which modulate carcinogenesis *in vitro*.

It is important to be aware of the limitations of preclinical study results when they are used to help design the clinical development of agents, such as resveratrol. As far as *in vitro* experiments are concerned, one might argue that they are often designed to hint at (rather than faithfully delineate) possible mechanisms of action and provide basic data which help attracting larger amounts or resources for animal studies. It is conceivable that ultimately, many of the mechanistic properties which have been elucidated for resveratrol are irrelevant for human cancer. Nevertheless, one should bear in mind that, as resveratrol was very expensive to produce, the animal studies would probably not have been conducted, if it had not been for the exhaustive *in vitro* database available, constituting a powerful impetus for further evaluation. In addition, the value of the rodent models used to evaluate the cancer chemopreventive efficacy of resveratrol needs to be critically scrutinized. The profound differences in efficacy seen, even in different studies using one model, as outlined above, cast doubt on their relevance for clinical studies. Potential pitfalls in the interpretation of results obtained in colorectal carcinogenesis models have recently been discussed in general terms in two point–counterpoint contributions to this journal (29, 30).

Nevertheless, it is beyond doubt that the development of cancer chemopreventive agents needs to be rationalized as much as possible exploiting all of the preclinical data available to facilitate scientific interpretation of clinical results and enable subsequent studies to improve intervention. In light of the wealth of preclinical data available on resveratrol, the basic question for its clinical development is clearly whether in a human Phase I study it is possible to achieve plasma levels at nontoxic doses that are close to those having shown efficacy in animal models, assuming that the pharmacokinetics are similar between the species. Therefore, it seems important to attempt resolution of the conundrum outlined above. How can it be resolved? There are a few possible explanations, and below we discuss four obvious ones: (*a*) does resveratrol perhaps accumulate in tissues in which malignancies have been shown to be prevented specifically in rats and not in other rodents? The pharmacokinetic analyses presented thus far do not support the contention that rats are characterized by unusually high concentrations of resveratrol in specific tissues when compared with, *e.g.*, mice. Furthermore, using the NMU-induced mammary tumor model in rats, Bhat *et al.* (22) required the more customary high dose of 100 mg/kg dose to prevent malignancy; (*b*) are the routes of administration used for resveratrol in the rat studies, in which it was found to be exquisitely potent, different from those used in other rodent studies, thus leading to exceptionally high tissue concentrations? This possibility can probably be discounted, because the agent seems to have been given in these studies in standard ways, by the *i.g.* or *i.p.* routes or admixed with the diet or the drinking water; (*c*) might resveratrol possess genuine high potency, which has hitherto been overlooked, via mechanisms thus far undiscovered in *in vitro* experiments? The history of anticancer drug discovery provides a good number of interesting examples of molecules, which, while causing cellular changes at vanishingly small concentrations, abolish these very effects at higher concentrations in the same biosystem, leading to a biphasic concentration-response relationship. A case in point is the partial protein kinase C agonist bryostatin 1, which inhibits lung cancer cell growth *in vitro* at concentrations as low as 1–10 nM but not at concentrations of ≥100 nM (31). It is just possible, but not very likely, that resveratrol behaves in an analogous fashion; and (*d*) are resveratrol metabolites effective modulators of carcinogenesis in their own right with activity in the 10–100 μM concentration range, which seems easily attainable *in vivo*? If resveratrol metabolites were to possess efficacy, they could conceivably contribute to, or account for, the efficacy of resveratrol *in vivo*. In that case, a lot of the extensive published data on the properties of resveratrol in cells *in vitro* would be rendered rather irrelevant with respect to explaining activity in animals and eventually in humans *in vivo*.

It seems essential that the rational planning of future

intervention trials of resveratrol in humans is preceded by the resolution of the flummoxing discrepancy between the concentration of resveratrol required for activity *in vitro* on the one side and the doses found to be efficacious *in vivo* in three papers on the other. In our view, the optimal path to its resolution should encompass the following four-pronged strategy: (*a*) additional efficacy studies of resveratrol in rodents *in vivo* should, as a priority, include measurement of parent compound and metabolites in the target tissues; (*b*) the bioavailability of resveratrol in humans needs to be determined; (*c*) metabolites of resveratrol should be characterized and quantitated in humans; (*d*) mechanistic *in vitro* studies should explore the activity of resveratrol at nanomolar concentrations and focus on resveratrol metabolites, especially its conjugates. Interestingly, piceatannol (3, 4, 3′,5′-tetrahydroxystilbene), a hydroxylated resveratrol cogener with greater ability to induce apoptosis in leukemia cells than resveratrol (32), was recently identified as a metabolite of resveratrol in suspensions of microsomes expressing cytochrome CYP1B1 (33). Yet, it is not known whether this species is generated *in vivo* in animals.

The successful advancement of clinical cancer chemoprevention requires new agents to be discovered and explored which have an unblemished toxicity record. Diet-derived polyphenols, such as resveratrol, with interesting cancer chemopreventive properties in experimental models, remain attractive as clinical candidates. One reason for their attractiveness is the fact that the long-proven use of their dietary sources suggests low potential for unwanted side effects, although this notion may not hold if they are administered at high doses as single agents. The resolution of the conundrum outlined here will eventually help optimize the clinical evaluation of resveratrol based on sound mechanistic, pharmacokinetic, and pharmacodynamic data. The results of forthcoming studies to resolve this conundrum will constitute a body of preclinical and clinical knowledge, which should provide a useful paradigm for the successful development of the whole class of naturally occurring cancer chemopreventive polyphenols.

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Cancer Epidemiol Biomarkers Prev 2003;12:953-957.