Cancer Chemopreventive Activity of Resveratrol, a Natural Product Derived from Grapes


Resveratrol, a phytoalexin found in grapes and other food products, was purified and shown to have cancer chemopreventive activity in assays representing three major stages of carcinogenesis. Resveratrol was found to act as an antioxidant and antimutagen and to induce phase II drug-metabolizing enzymes (anti-initiation activity); it mediated anti-inflammatory effects and inhibited cyclooxygenase and hydroperoxidase functions (antipromotion activity); and it induced human promyelocytic leukemia cell differentiation (antiproliferation activity). In addition, it inhibited the development of preneoplastic lesions in carcinogen-treated mouse mammary glands in culture and inhibited tumorigenesis in a mouse skin cancer model. These data suggest that resveratrol, a common constituent of the human diet, merits investigation as a potential cancer chemopreventive agent in humans.

Cancer is the largest single cause of death in both men and women, claiming over 6 million lives each year worldwide. Chemoprevention, the prevention of cancer by ingestion of chemical agents that reduce the risk of carcinogenesis (1), is one of the most direct ways to reduce morbidity and mortality. Cancer chemopreventive agents include nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, aspirin, piroxicam, and sulindac, all of which inhibit cyclooxygenase (COX) (2). This inhibitory activity is relevant to cancer chemoprevention because COX catalyzes the conversion of arachidonic acid to pro-inflammatory substances such as prostaglandins, which can stimulate tumor cell growth and suppress immune surveillance (3). In addition, COX can activate carcinogens to forms that damage genetic material (4).

In searches for new cancer chemopreventive agents over the past several years, hundreds of plant extracts have been evaluated for their potential to inhibit COX. An extract derived from Cascia quinquangulata Rich. (Leguminosae), collected in Peru, was identified as a potent inhibitor, and on the basis of bioassay-guided fractionation, resveratrol (3,5,4′-trihydroxy-trans-stilbene) (Fig. 1) was identified as the active principle (5).

The process of chemical carcinogenesis can be divided into three general stages, and chemopreventive agents have been categorized according to the stage that they inhibit (6). Resveratrol inhibits cellular events associated with tumor initiation, promotion, and progression. As noted above, the compound was identified on the basis of its ability to inhibit the cyclooxygenase activity of COX-1 (median effective dose $ED_{50} = 15 \mu M$) (Fig. 2A), and this activity correlates with antimutagen activity. Although its inhibitory activity was less than that of certain NSAIDs, such as indomethacin ($ED_{50} = 2.3 \mu M$) (Fig. 2A), it was much greater than that mediated by compounds such as aspirin ($ED_{50} = 880 \mu M$). Also, unlike indomethacin and most other NSAIDs, resveratrol inhibited the hydroperoxidase activity of COX-1 ($ED_{50} = 3.7 \mu M$) (Fig. 2B). Resveratrol-mediated inhibition was specific for the cyclooxygenase activity of COX-1 because there was no discernable activity when oxygen uptake was assessed with COX-2 (Fig. 2A), an inducible form of the enzyme associated with responses such as inflammation (7). In addition, inhibition of the hydroperoxidase activity of COX-2 ($ED_{50} = 85 \mu M$) was greatly reduced relative to the activity observed with COX-1.

On the basis of these results, we investigated the anti-inflammatory activity of resveratrol. In the carrageenan-induced model of inflammation in rats, resveratrol significantly reduced edema both in the acute phase (3 to 7 hours) and in the chronic phase (24 to 144 hours). The edema-suppressing activity of resveratrol was greater than that of phenylbutazone and was similar to that of indomethacin (Fig. 3). Overall, these data demonstrate the potential of resveratrol to inhibit tumor promotion.

Resveratrol was also found to inhibit events associated with tumor initiation. For example, resveratrol inhibited, in a dose-dependent manner, free-radical formation ($ED_{50} = 27 \mu M$) when human promyelocytic leukemia (HL-60) cells were treated with 12-O-tetradecanoylphorbol-13-acetate (TPA) (8). The compound also functioned as an antimutagen, as illustrated by its dose-dependent inhibition of the mutagenic response induced by treatment of Salmonella typhimurium strain TM677 with 7,12-dimethylbenz(a)anthracene (DMBA) ($ED_{50} = 4 \mu M$) (9). In addition, resveratrol induced quinone reductase activity with cultured mouse hepatoma (Hepa 1c1c7) cells (concentration required to double activity, 21 μM) (10), which is relevant because phase II enzymes, such as quinone reductase, are capable of metabolically detoxifying carcinogens (11). An identical response profile was observed with cultured BPC1 hepatoma cells (a derivative of Hepa 1c1c7 cells that is incapable of phase I enzyme induction), indicating that resveratrol is a multifunctional inducer.

We also tested the ability of resveratrol to inhibit the progression stage of carcino-

Fig. 1. Structure of resveratrol.
resveratrol merits further investigation as a cancer chemopreventive agent in humans. In light of the adverse health effects of long-term alcohol consumption, however, foods and nonalcoholic beverages derived from grapes (20) should be considered as alternative dietary sources.
Cortical neurons receive synaptic inputs from thousands of afferents that fire action potentials at rates ranging from less than 1 hertz to more than 200 hertz. Both the number of afferents and their large dynamic range can mask changes in the spatial and temporal pattern of synaptic activity, limiting the ability of a cortical neuron to respond to its inputs. Modeling work based on experimental measurements indicates that short-term depression of intracortical synapses provides a dynamic gain-control mechanism that allows equal percentage rate changes on rapidly and slowly firing afferents to produce equal postsynaptic responses. Unlike inhibitory and adaptive mechanisms that reduce responsiveness to all inputs, synaptic depression is input-specific, leading to a dramatic increase in the sensitivity of a neuron to subtle changes in the firing patterns of its afferents.

Synaptic Depression and Cortical Gain Control

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Cortical neurons transmit information by responding selectively to changes in the spatial and temporal pattern of presynaptic action potentials arriving at about 10,000 synapses. Extracting meaningful information from such a large and complex set of inputs presents a severe challenge. Presynaptic afferents fire action potentials at a wide variety of different rates, and signals carried by slowly firing afferents may be masked by random fluctuations in the activity of afferents firing at high rates. This problem can be avoided if cortical neurons monitor slowly firing afferents at high gain while reducing the gain for high-rate inputs. Such gain control cannot be achieved through fixed synaptic weights, because afferent firing rates change over time. We propose that short-term synaptic depression provides an automatic, dynamic gain-control mechanism. By balancing contributions

REFERENCES AND NOTES

5. Roots of C. quinquangulata Rich. (Leguminosae) were collected in Peru in 1974. The dried ground pound (30 mg, 0.003%) that was determined to be C14H12O3 by high-resolution mass spectral (MS) analysis. This compound was identified as resveratrol (4. T. V. Zenser et al., J. Pharmacol. Exp. Ther. 227, 545 (1987); D. Wild and H. G. Deegan, Carcinogenesis 8, 541 (1987).
8. S. Sharma, J. D. Stutzman, G. J. Kelloff, V. E. Steele, Cancer Res. 54, 5848 (1994).
11. J. A. Varela and S. B. Nelson, Department of Biology, Brandeis University, Waltham, MA 02254, USA.
12. J. A. Varela and Kamal Sen, Volen Center, Brandeis University, Waltham, MA 02254, USA.
15. Daily consumption of two to five glasses (or a maximum of 375 ml/day) of red wine may deliver a sufficient amount of resveratrol to alter arachidonic acid metabolism or other physiological responses depending on absorption, metabolism, and residence time within the blood circulation and relevant tissues (D. M. Goldberg, Clin. Chim. Acta 14, 14 (1966)). Resveratrol concentrations in other food products, such as grape juice, pomace, and purées are provided in B. J. Ector, J. B. Magee, C. P. Hegwood, and M. J. Coing [Am. J. Enol. Vitic. 47, 57 (1996)].