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Ebselen, a useful tool for understanding cellular redox biology and a promising drug candidate for use in human diseases

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ABSTRACT

Ebselen is an organoselenium compound with glutathione peroxidase (GPx)-like hydroperoxide reducing activity. Moreover, ebselen has its own unique reactivity, with functions that GPx does not have, since it reacts with many kinds of thiols other than glutathione. Ebselen may affect the thioredoxin systems, through which it may contribute to regulation of cell function. With high reactivity toward thiols, hydroperoxides, and peroxynitrite, ebselen has been used as a useful tool in research on cellular redox mechanisms. Unlike α-tocopherol, ebselen does not scavenge lipid peroxyl radicals, which is another advantage of ebselen for use as a research tool in comparison with radical scavenging antioxidants. Selenium is not released from the ebselen molecule, which explains the low toxicity of ebselen. To further understand the mechanism of cellular redox biology, it should be interesting to compare the effects of ebselen with that of selenoprotein P, which supplies selenium to GPx. New medical applications of ebselen as a drug candidate for human diseases such as cancer and diabetes mellitus as well as brain stroke and ischemia will be expected.

1. Prologue

It was the organoselenium compound ebselen (2-phenyl-1,2-benzisoselenazol- 3(2H)-one; PZ-51, DR-3305) that provided the occasion for my first meeting with Dr. Sies. At the First International Congress on Vitamins and Biofactors in Life Science which was held in Kobe Japan in September 1991, I presented a poster entitled “Reaction of ebselen as an antioxidant against lipid peroxidation”. At that time, Dr. Sies asked me several questions and gave me many valuable suggestions (Fig. 1).

Ebselen has a long history which takes us back to the early 1970s. Parnham and Sies have described this history dramatically in their commentary, which has been published in the literature [1]. Five scientists who were all employed by the same company at the time—Eugen Etschenberg, Norbert Dereu, Axel Romer, Mike Parnham, and Erich Graf—played important roles in the development of ebselen as a candidate for clinical use. Erich Graf was the person who contacted Helmut Sies to ask him to test ebselen in a model of oxidative stress set up by Enrique Cadenas. During this period, there were a number of encouraging findings and reports from academia that tended to favor the proponents of ebselen. For example, Leopold Flohe showed that the hydroperoxide-reducing enzyme glutathione peroxidase (GPx) contained selenium at its active site [2]. This discovery sparked new research into reactive oxygen species, glutathione, and selenium, and thus of course of ebselen. In 1984, the GPx-like activity of ebselen was established; that is, it was demonstrated that ebselen catalyzes the reduction of hydroperoxides in a glutathione-dependent manner [3]. The mechanism for the thiol-dependent catalytic reduction of hydroperoxide by ebselen was published in 1987 [4]. This mechanism has since been reconfirmed by many researchers [5–8].

It was found that selenium from ebselen was not incorporated into GPx [3,9,10] because of no release of selenium from ebselen molecule, which allayed any concern that may have existed regarding the possible toxicity of ebselen.

In parallel with the advances being made in academic research on ebselen, advances were also being made internationally in its commercial development. The Daiichi Pharmaceutical Company of Japan was one of the companies which carried out clinical trials. At the time that these clinical trials were being held (during the 1980s and 1990s), the frequent meetings which were held in Japan, Germany, the US, and France were always exciting to attend.

I joined to the laboratory of Etsuo Niki in Tokyo Japan in February 1991. Ebselen was the compound that I first studied in Niki's laboratory. We studied the action of ebselen as an antioxidant

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Fig. 1. Dr. Helmute Sies and myself in front of my poster at Kobe in September 1991. The cameraman was Dr. Etsuo Niki.

under various conditions. We obtained ebselen thanks to the kindness of Hiroyuki Masayasu of Daiichi Pharmaceutical, who was what Niki and I used to refer to as a genuine "ebselen man." Masayasu was enthusiastic about developing ebselen as a novel therapeutic drug for stroke patients.

During this time period, whenever I met Dr. Sies at a scientific conference, we would discuss ebselen. He always provided encouragement to me by saying that ebselen was an excellent and promising compound, and was a deserving candidate to become a novel drug. This inspired in me not just confidence, but I have to say also a little ambition, and the more I reflected on Dr. Sies's words the more his face began, in my mind, to overlap that of Yukichi Fukuzawa, whose face is printed on the Japanese ten-thousand yen bill, the largest-denomination bill in circulation in Japan.

Unfortunately, our dream has not come true, since the reviewers at the Japanese regulatory authority, the Ministry of Health, Labour and Welfare considered the efficacy of ebselen to be insufficient for use as a drug to treat cerebral ischemia. And so along with the elusive dream of government approval for ebselen, the images of Yukichi Fukuzawa, Brothers Grimm, Benjamin Franklin, and P. & M. Curie, which I had been looking forward to seeing in our budget, have all gone somewhere else.

2. Functions of ebselen

2.1. GPx mimic/hydroperoxide reduction

Ebselen reduces hydroperoxides including hydrogen peroxide, phospholipid hydroperoxide, and cholesterol ester hydroperoxide [11–14] by GPx mimic action. Briefly, enzymatic catalysis of hydroperoxide reduction involves enzyme-bound selenocysteine (E-CysSeH, selenol) and proceeds by the following three steps: (1) hydrogen peroxide or organic hydroperoxide (ROOH) reacts with selenol (E-CysSeH) to yield selenenic acid (E-CysSeOH) and the corresponding alcohol (ROH); (2) E-CysSeOH is then reduced by GSH, E-CysSeOH reacting with GSH to give the selenosulfide (E-CysSe-SG) and H_2O; and (3) reaction of this with another GSH to regenerate E-CysSeH and oxidized glutathione (GSSG). The overall reaction; i.e., reduction of hydroperoxide and oxidation of GSH, is shown at (4). Although not shown at the Formulas below, GSSG is reduced back to GSH by glutathione reductase with consumption of NADPH.

$$\text{E-CysSeH} + \text{ROOH} \rightarrow \text{E-CysSeOH} + \text{ROH} \quad (1)$$

$$\text{E-CysSeOH} + \text{GSH} \rightarrow \text{E-CysSe-SG} + \text{H}_2\text{O} \quad (2)$$

$$\text{E-CysSe-SG} + \text{GSH} \rightarrow \text{E-CysSeH} + \text{GSSG} \quad (3)$$

$$\text{ROOH} + 2\text{GSH} \rightarrow \text{ROH} + \text{H}_2\text{O} + \text{GSSG} \quad (4)$$

Maiorino et al. showed that the mechanism of catalysis of the GPx-like reaction of ebselen appeared to be kinetically identical to that of the ter uni ping–pong enzyme reaction [15]. However, in addition to ebselen selenol (ebselen-SeH) and ebselen selenylsulfide (ebselen-Se-SG), metabolites such as ebselen selenoxide (ebselen-Se=O) and ebselen diselenide (ebselen-Se-Se-ebselen) have been detected which are assumed to be putative intermediates in the reaction of ebselen, suggesting that the catalytic reaction of ebselen is more complicated [16].

2.2. Ebselen in the thioredoxin system

Ebselen affects the thioredoxin (Trx) system [17–19]. Ebselen is reduced to ebselen selenol (ebselen-SeH) by the action of Trx reductase (TR) with consumption of NADPH, which is enhanced in

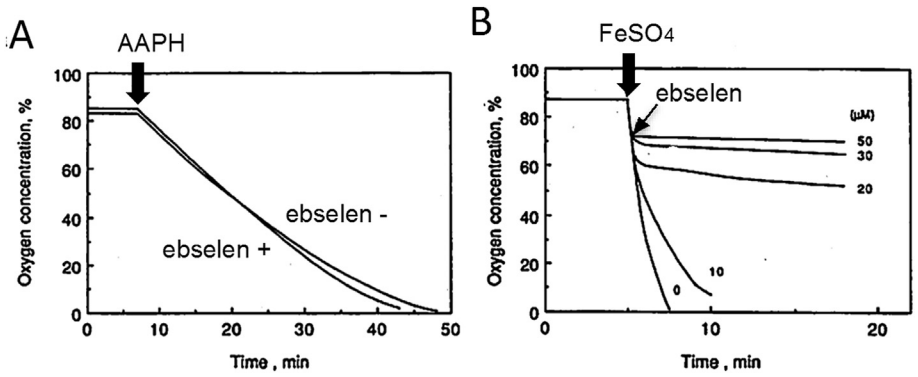

Fig. 2. Oxidation of methyl linoleate emulsions in aqueous dispersions induced by AAPH (A) or $FeSO_4$ (B) in the absence or presence of ebselen at 37 °C in air. (Noguchi et al., Biochem. Pharmacol. 44, 39–44, 1992).