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Review

7-Hydroxycholestrol as a possible biomarker of cellular lipid peroxidation: Difference between cellular and plasma lipid peroxidation

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ABSTRACT

Polyunsaturated fatty acids and their esters are known to be susceptible to free radical-mediated oxidation, whereas cholesterol is thought to be more resistant to oxidation. In fact, it has been observed that in the case of plasma lipid peroxidation, the amount of oxidation products of polyunsaturated fatty acids such as linoleic acid was higher than that of cholesterol. In contrast, during oxidative stress-induced cellular lipid peroxidation, oxidation products of cholesterol such as 7-hydroxycholesterol (7-OHCh) were detected in greater amounts than those of linoleates such as hydroxyoctadecadienoic acid (HODE). There are several forms of oxidation products of cholesterol and linoleates *in vivo*, namely, hydroperoxides, as well as the hydroxides of both the free and ester forms of cholesterol and linoleates. To evaluate these oxidation products, a method used to determine the lipid oxidation products after reduction and saponification was developed. With this method, several forms of oxidation products of cholesterol and linoleates are measured as total 7-OHCh (t7-OHCh) and total HODE (tHODE), respectively. During free radical-mediated lipid peroxidation in plasma, the amount of tHODE was 6.3-fold higher than that of t7-OHCh. In contrast, when Jurkat cells were exposed to free radicals, the increased amount of cellular t7-OHCh was 5.7-fold higher than that of tHODE. Higher levels of t7-OHCh than those of tHODE have also been observed in selenium-deficient Jurkat cells and glutamate-treated neuronal cells. These results suggest that, in contrast to plasma oxidation, cellular cholesterol is more susceptible to oxidation than cellular linoleates. Collectively, cholesterol oxidation products at the 7-position may be a biomarker of cellular lipid peroxidation.

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Abbreviations: AIPH, 2,2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride; Ch, cholesterol; CE-OH, cholesteryl ester hydroxide; CE-OOH, cholesteryl ester hydroperoxide; GSH, glutathione; GPx, glutathione peroxidase; HODE, hydroxyoctadecadienoic acid; HPODE, hydroperoxyoctadecadienoic acid; L, linoleates; LDL, low density lipoprotein; PBS, phosphate-buffered saline; PC-OH, phosphatidylcholine hydroxide; PC-OOH, phosphatidylcholine hydroperoxide; PH-GPx, phospholipid hydroperoxide glutathione peroxidase; PLPC, 1-palmitoyl-2-linoleoyl-sn-glycero-3-phosphatidylcholine; PUFA, polyunsaturated fatty acid; Sec, selenocysteine; TR, thioredoxin reductase; 7-KCh, 7-ketocholesterol; 7-OHCh, 7-hydroxycholesterol; 7-OOHCh, 7-hydroperoxicholesterol.

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1. Introduction

Lipid peroxidation has been the subject of extensive studies for several decades, and its mechanism, dynamics, and products are well described [1]. Lipid peroxidation produces potentially toxic compounds, but it has also been demonstrated that lipid peroxidation products may act as signaling mediators and induce an adaptive response [2,3]. It is well known that polyunsaturated fatty acids (PUFA) and their esters are vulnerable to oxidation and that their susceptibility to oxidation increases with an increase in the number of double bonds [1]. Cholesterol, another important lipid *in vivo*, is oxidized to produce versatile products termed oxysterols [4]. PUFA and cholesterol are oxidized both enzymatically and non-enzymatically; however, cholesterol, unlike PUFA, does not possess bis-allylic hydrogens and has been considered to be less susceptible to free radical-mediated oxidation than polyunsaturated lipids [5].

Lipid hydroperoxides, the primary products of lipid peroxidation, are not stable end products. Instead, they are good substrates for many enzymes such as glutathione peroxidases (GPx) and phospholipases, and they also undergo non-enzymatic secondary reactions [1,6]. It should be noted that the amount of lipid peroxidation products found in biological fluids and tissues depends on the rates of metabolism and clearance, as well as formation. Therefore, consideration of the metabolism of oxidized cholesterol and linoleates is important to the understanding of lipid peroxidation *in vivo*. Yoshida et al. have developed a method to measure the levels of lipid peroxidation *in vivo*, where total 7-hydroxycholesterol (t7-OHCh) and total hydroxyoctadecadienoic acid (tHODE) can be determined from biological samples after reduction with triphenylphosphine and saponification by potassium hydroxide [7,8]. The cholesterol oxidation products, which are oxidized at the 7-position, such as 7β-hydroxy- (7β-OHCh), 7α- and 7β-hydroperoxy-, and 7-ketocholesterol (7-KCh) are generated by non-enzymatic oxidation, whereas 7α-hydroxycholesterol (7α-OHCh) is generated by both enzymatic and non-enzymatic oxidation [4]. In this assay with reduction and saponification, oxysterols such as 7-hydroperoxycholesterol (7-OOHCh) and 7-OHCh are measured as t7-OHCh. tHODE is the sum of the following four isomers: 9- and 13-(Z,E)-HODEs; and 9- and 13-(E,E)-HODEs. Oxidation by 12/15-lipoxygenase proceeds via regio-, stereo-, and enantio-specific mechanisms to yield 13S-hydroperoxy-9Z, 11E-octadecadienoic acid (13(S)-(Z,E)-HPODE) exclusively, whereas singlet oxygen-mediated oxidation yields 9-, 10-, 12-, and 13-(Z, E)-HPODE. In contrast, oxidation of linoleates induced by free radicals yields all of the four isomers, namely, 9- and 13-(Z,E)- and 9- and 13-(E,E)-HPODEs as the primary products. HPODEs are readily reduced *in vivo* by reducing enzymes to give HODE. Therefore, 9- and 13-(E,E)-HODE are generated specifically when using free radical-mediated oxidation [9].

2. Plasma lipid peroxidation

It has been known that cholesterol is less susceptible to free radical-mediated oxidation than PUFAs such as linoleic acid. In fact, it has been reported that during low-density lipoprotein (LDL) oxidation, cholesterol is oxidized only after most PUFA esters have been oxidized [5]. It has also been reported that in the case of plasma lipid peroxidation initiated by free radical exposure, the amount of tHODE generated was 6.3-fold higher than that of t7-OHCh [10]. In a previous study, the amount of tHODE measured in free radical-exposed plasma was nearly identical to the sum of phosphatidylcholine hydroxide (PC-OH) and hydroperoxide (PC-OOH); and cholesteryl ester hydroxide (CE-OH) and hydroperoxide (CE-OOH), suggesting that the linoleates in PC and CE are the major sources of tHODE. Human plasma contains more CE than cholesterol; the ratio of CE to cholesterol is 4.1 [10]. Based on this report, the ratio of total cholesterol (tCh) to total linoleates (tL) with reduction and saponification of plasma lipids was calculated to be 4.36 (Table 1). In the plasma, when lipid peroxidation was induced by free radical exposure, the ratio of t7-OHCh to tHODE was calculated to be 0.16. Therefore, the molar relative oxidizability of plasma cholesterol to linoleates, (t7-OHCh/tHODE)/(tCh/tL), was calculated to be 0.04. These values are shown in Table 1 and Fig. 1 to compare the difference between plasma and cellular lipid peroxidation.

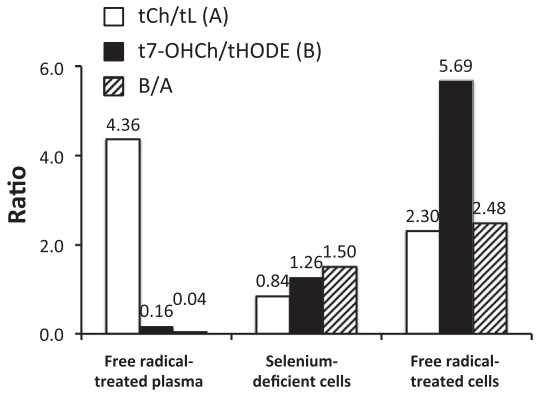

Fig. 1. The ratio of lipid peroxidation products and their substrates in plasma and cells. The ratios of total cholesterol (tCh) and total linoleates (tL) with reduction and saponification in each sample (A), t7-OHCh and tHODE obtained from each oxidized sample (B) were plotted. The molar relative oxidizability of cholesterol to linoleates obtained from (t7-OHCh/tHODE)/(tCh/tL) was also plotted (B/A).

Table 1
The amounts and the ratios of lipid peroxidation products and these substrates in plasma and cells.[a]

	Free radical-treated plasma [10]		Selenium-deficient Jurkat cells [15]	Free radical-treated Jurkat cells [15]	Glutamate-treated neuronal cells [19]	Free radical-treated erythrocytes [10]		PLPC and FC (model compounds) [10]		
	In PBS	In tBuOH/ACN				In PBS	In MeOH	In benzene	In tBuOH/ACN	In MeOH
tCh[b]	6.54	6.54	12.8	24.6	109.00	4.8	4.8	5	5	5
tL[b]	1.50	1.50	15.2	10.7	–	1.1	1.1	5	5	5
tCh/tL	4.36	4.36	0.84	2.30	–	4.4	4.4	1.0	1.0	1.0
t7-OHCh[c]	–	–	22.5	1133.00	43.00	–	–	–	–	–
tHODE[c]	–	–	17.8	199.00	0.15	–	–	–	–	–
t7-OHCh/tHODE	0.16	0.83	1.26	5.69	286.67	3.70	3.70	0.09	0.29	0.45
(t7-OHCh/tHODE)/(tCh/tL)	0.04	0.19	1.50	2.48	–	0.85	0.85	0.09	0.29	0.45

[a] Each data is referred from indicated Ref. in each column.
[b] mM in plasma, erythrocytes, and model compounds; nmol/mg protein in cells.
[c] pmol/mg protein.

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