**Induction of Cystine and Glutamate Transport Activity in Human Fibroblasts by Diethyl Maleate and Other Electrophilic Agents**

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The transport activity for cystine and glutamate in cultured human diploid fibroblasts is enhanced in response to diethyl maleate treatment. The enhancement is time- and dose-related, with a lag of about 3 h, and maximum enhancement (approximately 3-fold increase in the rate of uptake) is attained after 1 to 2 days of incubation of the cells with 0.1 mM diethyl maleate. The enhancement of the transport activity is accompanied by an increase in the V_{max} and little change in the K_{m}, and it requires RNA and protein synthesis. Other electrophilic agents, such as cyclolhex-2-en-1-one, ethacrynic acid, 1,2-epoxy-3-(p-nitrophenoxy)propane, and sulfobromophthalein, similarly enhance the transport activity. These electrophiles are known as agents that interact with glutathione. For example, diethyl maleate at high concentrations, i.e. 1 mM, depletes intracellular glutathione and injures the cells. However, at relatively low concentrations diethyl maleate and other electrophilic compounds do cause increases in the intracellular levels of glutathione which we attribute to the enhanced uptake of cystine. It is suggested that the transport system for cystine and glutamate is involved in a protective mechanism of cells against an electrophilic attack.

**EXPERIMENTAL PROCEDURES**

**Materials—** L-[3,4-3H]Cystine and L-[2,3-3H]Glutamic acid were obtained from Amersham and New England Nuclear, respectively. Diethyl maleate, ethyl cinnamate, ethyl sorbate, 1,2-epoxyethylbenzene, and p-nitrobenzyl chloride were from Wako Chemical Co.; 1,2-dichloro-4-nitrobenzene from Tokyo Kasei Co.; cyclolhex-2-en-1-one and 5-methylcyclolhex-2-en-1-one from Aldrich; ethacrynic acid and sulfobromophthalein from Sigma; 1,2-epoxy-3-(p-nitrophenoxy)propane from Eastman; 6-diazo-5-oxo-L-norleucine from Calbiochem. Vitamin E was a gift from Eisai Pharmaceutical Co. (Tokyo).

**Cell Culture—** The cells used in this study were human diploid fibroblasts derived from fetal lung (strain HAIN-6). They were cultured in Eagle's basal medium supplemented with 10% fetal calf serum. Cystine-free medium is similar to Eagle's basal medium except that it lacks cystine. One lot of serum containing no free cysteine was used for the cysteine-free medium. Vitamin E was dispersed in the cysteine-free medium at 2 μg/ml with the aid of sonifier, in order to prevent death of the cells in the medium (12).

**Uptake Method—** Amino acid uptake was measured by techniques described previously (2). Following culture of the cells in a 35-mm diameter plastic Petri dish, the cells were rinsed three times in warmed 10 mM phosphate-buffered saline, pH 7.4. Then the cells were incubated in 0.5 ml of the warmed uptake medium for specified time periods at 37°C. The uptake medium consisted of the same buffer used to rinse the cells plus labeled amino acid (1 μCi/0.5 ml). The incubations were terminated by rapidly rinsing the dishes three times in ice-cold phosphate-buffered saline, and the radioactivity was determined as described before. The rates of uptake were determined under conditions approximating initial rates, i.e. by taking the values for the 2-min uptake of cystine or glutamate.

**Determination of Glutathione—** Cells in a 35-mm diameter dish were rinsed three times in 10 mM phosphate-buffered saline, and glutathione was extracted with 1 ml of 5% trichloroacetic acid. The acid extract was taken up and treated four times with volumes of 0.01 N HCl-saturated diethyl ether. The resulting solution was used for the assay of total glutathione (reduced and oxidized glutathione), or it was incubated with 0.1 μmol of N-ethylmaleimide for 30 min followed by removal of excess N-ethylmaleimide by ether extraction as described above and used for the assay of oxidized glutathione.
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Glutathione was measured enzymatically by the method of Tietze (13).

RESULTS

Effect of Diethyl Maleate on the Cystine and Glutamate Uptake—Diethyl maleate was added to the culture of human diploid fibroblasts, and, after various intervals of incubation, the cells were washed and assayed for the uptake of cystine and glutamate. The rates of uptake were determined by taking the values for the 2-min uptake. As shown in Fig. 1, the addition of 0.1 mM diethyl maleate resulted in increases in the rate of uptake of cystine and glutamate. The effect was time-dependent, with a lag of about 3 h. A maximum stimulation, i.e. 2 to 3 times that of control, was attained after a day or two. It is noted that the uptake medium does not contain diethyl maleate. Direct addition of diethyl maleate to the uptake medium had no effect on the uptake. Fig. 2 shows the effect of a short time exposure of the cells to diethyl maleate on the uptake of cystine. The cells were incubated with diethyl maleate for 1 or 3 h, and then the medium was replaced by that containing no diethyl maleate. When the cells were exposed to diethyl maleate for as long as 1 h, the stimulatory effect of diethyl maleate on the cystine uptake appeared only slight. When the cells were incubated with diethyl maleate for 3 h, the uptake of cystine was enhanced for the following 6 h.

Fig. 3 shows enhancement of cystine uptake of the cells incubated for 24 h with various concentrations of diethyl maleate. The uptake was significantly enhanced by diethyl maleate even at 0.005 mM, and a maximum stimulation was
Effect of inhibitors of macromolecular synthesis on the diethyl maleate-induced enhancement of cystine or glutamate uptake

| Compound                      | Concentration | Cystine uptake
|-------------------------------|---------------|----------------|
|                               | mM            | % increase    |
| Cyclohex-2-en-1-one           | 0.025         | 120           |
|                               | 0.05          | 191           |
| 3-Methylcyclohex-2-en-1-one   | 0.05          | 24            |
|                               | 0.5           | 127           |
| Cyclohexanone                 | 1             | 14             |
| Ethacrynate                   | 0.05          | 188           |
|                               | 0.1*          | 214           |
| Maleate                       | 1             | 32            |
|                               | 2             | 100           |
| Fumarate                      | 1             | -3            |
|                               | 2             | 9             |
| Maleic hydrazide              | 1             | -2            |
| Ethyl cinnamate               | 0.1           | 14            |
|                               | 0.2*          | 43            |
| Ethyl sorbate                 | 0.5           | 25            |
|                               | 1*            | 45            |
| Diethyl succinate             | 1             | 6             |
| 1,2-Epoxyethylbenzene         | 0.2           | 76            |
|                               | 0.5*          | 91            |
| 1,2-Epoxy-3-(p-nitrophenoxy)propane | 0.05 | 41 |
|                               | 0.1*          | 101           |
| 1,2-Dichloro-4-nitrobenzene   | 0.2           | 21            |
|                               | 0.5*          | 44            |
| p-Nitrobenzyl chloride        | 0.01          | 31            |
|                               | 0.02*         | 61            |
| Sulfoxobromophthalein         | 0.1           | 107           |
|                               | 0.25*         | 172           |
| Acetamidophenol               | 1             | 1             |
| Acetylsaliclycide             | 1             | 4             |
| Salicylate                    | 1             | 0             |
| Bromobenzene                  | 0.2*          | 3             |
| Phenoborbital                 | 1             | 3             |
| 6-Diazox-5-oxo-L-norleucine   | 1*            | 5             |
| 2,4-Dinitrophenol             | 0.1           | 0             |
|                               | 0.5*          | -24           |
| Potassium cyanide             | 1             | 1             |
| Sodium azide                  | 0.1           | 0             |
|                               | 0.5           | -31           |

Note: *Cells were incubated in the medium for 24 h.

The cystine uptake was measured after cells were incubated with the compound for 24 h. Values are averages of two to four experiments.

The above results suggest an induction of cystine-glutamate transport activity by diethyl maleate. To examine a role of RNA and protein synthesis for the enhancement of cystine and glutamate uptake by diethyl maleate, actinomycin D or cycloheximide was added to the cells simultaneously with diethyl maleate, and after 24 h the rate of cystine and glutamate uptake was measured. Results in Table I show that both actinomycin D and cycloheximide completely blocked the increase in uptake by diethyl maleate. In these fibroblasts, actinomycin D at 0.1 μg/ml inhibited RNA synthesis by about 90%, which was measured by incorporation of labeled uridine into acid-insoluble material. Cycloheximide at 1 μg/ml inhibited protein synthesis, measured by incorporation of labeled leucine, by more than 80%.

The uptake of other amino acids was also examined to determine the specificity of the enhancement by diethyl maleate; there was little, if any, change in the rate of uptake of alanine, leucine, aspartate, and lysine by the cells incubated with 0.1 mM diethyl maleate for 24 h (data not shown).

Effect of Other Electrophilic Agents on the Cystine Uptake—Various compounds were tested to see whether they enhanced the cellular uptake of cystine. The cells were incubated with the compound for 24 h and the rate of uptake of cystine was measured (Table II). Cyclohex-2-en-1-one, 3-methylcyclohex-2-en-1-one, ethacrynate, maleate, ethyl cinnamate, and ethyl sorbate contain activated double bonds and have stimulated the cysteine uptake. Cyclohex-2-en-1-one and its 3-methyl derivative were powerful stimulators, but the former was effective at much lower concentration than the latter. Effect of maleate was manifested at 2 mM, whereas its diethyl ester exerted the similar effect at about 0.02 mM (Fig. 3). Fumarate and maleic acid hydrazide, double bonds of which are less activated than those of maleate, did not affect the uptake of cystine. Cyclohexanone and diethylsuccinate are structural analogues of cyclohex-2-en-1-one and diethyl maleate, respec-
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**Fig. 6. Changes in intracellular glutathione levels by diethyl maleate.** A, time course of changes in cellular glutathione after addition of 0.1 mM (○) or 1 mM (□) diethyl maleate. B, glutathione levels of the cells exposed to various concentrations of diethyl maleate for 24 h. Total glutathione (reduced and oxidized) was measured. The data are the averages ± S.D. of two experiments with duplicate assays for each.

**TABLE III**

Changes in intracellular glutathione contents by some electrophilic agents

Glutathione was determined after cells were incubated with the compound for 24 h. Values are averages ± S.D. of two to four experiments.

| Compound                  | Concentration | Glutathione content |
|---------------------------|---------------|---------------------|
|                           | mM            | % increase          |
| Cyclohex-2-en-1-one       | 0.01          | 23 ± 3              |
|                           | 0.025         | 52 ± 3              |
|                           | 0.04          | 36 ± 2              |
| 3-Methylcyclohex-2-en-1-one| 0.05          | 10 ± 3              |
|                           | 0.5           | 28 ± 9              |
|                           | 1             | 47 ± 10             |
| Ethacrynate               | 0.05          | 59 ± 19             |
|                           | 0.1           | 102 ± 5             |
| Maleate                   | 1             | 39 ± 4              |
|                           | 2             | 60 ± 1              |
| Fumarate                  | 1             | 5 ± 2               |
|                           | 2             | 3 ± 1               |
| Ethyl cinnamate           | 0.1           | 9 ± 2               |
|                           | 0.2           | 30 ± 6              |
| 1,2-Epoxyethylbenzene     | 0.2           | 57 ± 4              |
|                           | 0.5           | 118 ± 2             |
| 1,2-Epoxy-3-(p-nitrophenox)propionate | 0.05 | 67 ± 1 |
|                           | 0.1           | 114 ± 6             |
| p-Nitrobenzyl chloride    | 0.01          | 57 ± 5              |
|                           | 0.02          | 109 ± 8             |
| Sulfobromophthalein       | 0.1           | 126 ± 11            |
|                           | 0.25          | 165 ± 10            |

Epoxy compounds, dichloronitrobenzene, p-nitrobenzyl chloride, and sulfobromophthalein are electrophilic compounds, and they have enhanced the cystine uptake. Aromatic compounds, such as acetaminophenol, acetylsalicylate, salicylate, and bromobenzene, have no electrophilic center and they have not stimulated the uptake. Phenobarbital is known to induce the synthesis of some specific proteins, but it did not enhance the cystine uptake. Some metabolic inhibitors were also examined. Potassium cyanide and an inhibitor for

tively, except that they do not have unsaturated double bonds. These analogues did not enhance the cystine uptake. It is, therefore, suggested that the stimulatory effect of the compounds depends on the reactivity of their double bonds.

**TABLE IV**

Effect of amino acid inhibitors (2.5 mM) of cystine uptake on the increase in glutathione induced by 0.1 mM diethyl maleate

| Addition to the incubation medium | Glutathione* | Uptake of cystine (0.05 mM)** |
|----------------------------------|--------------|------------------------------|
| None                             | 28.1 ± 1.3   | 0.71 ± 0.21                  |
| Diethyl maleate                  | 53.5 ± 6.2   | 2.09 ± 0.20                  |
| Diethyl maleate + glutamate      | 23.1 ± 4.0   | 6.28 ± 0.92 (2.41 ± 0.18)    |
| Diethyl maleate + homocysteate   | 11.7 ± 0.3   | 0.13 ± 0.01 (2.18 ± 0.08)    |
| Diethyl maleate + aspartate      | 52.5 ± 2.7   | 1.87 ± 0.10 (2.04 ± 0.16)    |

*Cells were incubated in the medium for 24 h.

**TABLE V**

Effect of diethyl maleate and starvation with respect to cystine on the uptake of cystine

| Incubation medium | Uptake of cystine (0.05 mM)** |
|-------------------|-------------------------------|
| 24 h^a            | 0.75 ± 0.06 0.76 ± 0.10       |
| 48 h^a            | 1.99 ± 0.19 2.16 ± 0.18       |
| Complete medium   | 2.02 ± 0.22 2.22 ± 0.08       |
| Cystine-free medium | 1.77 ± 0.23 2.05 ± 0.25       |
| Cystine-free medium + diethyl maleate (0.05 mM)^a | 2.97 ± 0.03 3.06 ± 0.15 |

^aThe results are the averages ± S.D. of two experiments with duplicate assays for each.

^bIncubation time.

^cEagle's basal medium supplemented with 10% fetal calf serum.

^dWhen diethyl maleate concentration in cystine-free medium was elevated to 0.1 mM, many cells were degenerated within 24 h.
Changes in Glutathione Content—It may be reasonably assumed that the electrophilic agents described above principally interact with sulfhydryl groups of the cells, especially with glutathione, the major nonprotein sulfhydryl compound in the cells. Fig. 6A shows changes in the intracellular levels of glutathione when cells are exposed to 0.1 or 1 mM diethyl maleate. Diethyl maleate at 1 mM rapidly depleted cellular glutathione, and at 9 h after the addition of diethyl maleate, the cells started to die. Essentially no glutathione was detectable in the cells at 12 h, and no viable cells were found at 24 h. In contrast, when the cells were exposed to 0.1 mM diethyl maleate, the glutathione content, though decreased slightly for the first 3 h, increased and became twice as much as that of control cells after 24 h. Diethyl maleate caused the increase in glutathione over the wide concentration range (Fig. 5B).

In these experiments total glutathione (reduced and oxidized) was measured. In a typical case, both total and oxidized glutathione contents were separately determined as described under "Experimental Procedures." The percentage of oxidized glutathione to the total glutathione was 0.9% (±0.2%, average of three experiments) in the normal cells, and when the cells were treated with 0.05-0.1 mM diethyl maleate for 24 h, it was 0.6% (±0.1%). Contents of sulfhydryl groups in these samples were also determined using 5,5'-dithiobis-(2-nitrobenzoic acid), and they were nearly equal to the contents of total glutathione. The results indicate that almost all glutathione measured is reduced-form glutathione and that the increase in glutathione by diethyl maleate is due to the increase in reduced-form glutathione, not in oxidized glutathione.

The effect of other electrophilic agents on the glutathione levels is described in Table III. Generally, the increase in glutathione by these agents was dose-dependent in a manner similar to the enhancement of cystine uptake, although the increase in glutathione content did not completely correlate with the enhanced activity of cystine uptake. Cyclohex-2-en-1-one and its methyl derivative, which were potent inducers for cystine uptake, did not elevate so much the glutathione content.

It is likely that the increase in the glutathione content caused by some electrophilic agents results largely from the enhanced uptake of cystine because cystine in the culture medium is a major source of cellular cysteine which is a rate-limiting amino acid in glutathione synthesis. To test this possibility, effect of inhibitors of the cystine uptake on the intracellular glutathione levels was examined. Glutamate and homocysteate are substrates for the cystine-glutamate transport system and, therefore, they competitively inhibit the uptake of cystine. These amino acids, when added to the culture medium along with diethyl maleate, completely blocked the increase in glutathione caused by diethyl maleate (Table IV). Under these conditions the cystine-glutamate transport system itself was enhanced by diethyl maleate to the same extent as that of the control (no extra amino acid added). However, the actual uptake of cystine into the cells was greatly reduced by the inhibitory action of glutamate or homocysteate (Table IV). Aspartate is not an inhibitor of cystine-glutamate system, and it had little effect on the increase in glutathione by diethyl maleate. The results are consistent with the view that the increase in the cellular glutathione by diethyl maleate is attributable to the increased rate of uptake of cystine.

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the enhancement of the cystine-glutamate system. It seems of importance to search for something in common in effects of the electrophilic agents and the starvation in cystine.

The cystine-glutamate transport system is first found in human fibroblasts (2) and then in rat hepatoma cell line (17) and rat hepatocytes in primary culture (18). Whether the activity of the system in hepatic cells is induced by electrophilic agents is of interest and now under study.

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