Normalization of Intracellular Lysosomal Hydrolases in I-cell Disease Fibroblasts with Sucrose Loading*

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I-cell disease (ICD) is an hereditary inborn error of metabolism by lysosomal storage due to the multiple lysosomal hydrolases deficiency. Many inclusion materials are seen by phase contrast microscopy in cultured skin fibroblasts from the patients with ICD.

We recently reported that the addition of 88 mM sucrose to the medium of cultured human skin fibroblasts from normal subjects induced several lysosomal hydrolases, but did not induce deficient hydrolases in lysosomal enzyme deficiencies (Kato, T., Okada, S., Ohshima, T., Inui, K., Yutaka, T., and Yabuuchi, H. (1981) Biochem. Int. 3, 551-556). This time sucrose loading was applied to the cultured skin fibroblasts from the patients with ICD. Incubation with 88 mM sucrose for more than 10 days exhibited significant effects. Biochemically, the activities of deficient hydrolases reached their normal levels, and morphologically, typical inclusion materials disappeared. These results indicate that sucrose enhanced synthesis of normal lysosomal enzymes and lysosome functions were normalized in ICD fibroblasts.

I-cell disease (Mucolipidosis II) is a generalized neurodegenerative disease in childhood, transmitted by an autosomal recessive trait, clinically similar to the mucopolysaccharidoses, but usually with normal urinary excretion of mucopolysaccharides (1-4). The disease owes its name to many inclusions that are seen by phase contrast microscopy in the cultured skin fibroblasts from the patients with ICD (1, 2). These inclusions have been identified electron microscopically as lysosomes filled with membrane fragments and other debris (2, 5, 6). ICD is characterized by decreased activities of most of acid hydrolases in cultured fibroblasts, with concomitant increases of many of these enzyme activities in the fibroblast medium (7, 8). ICD offers a unique opportunity to study the kinetics of lysosomal hydrolases (9-13).

Since De Duve and Wattiaux (14) described sucrose-induced vacuolation of cells, many studies have been published on the effects of sucrose on the cultured mammalian cells (15-17). The experimental period was relatively short in their studies, i.e., 3 days at the longest (16). Therefore, it is assumed that they have not fully investigated the effects of sucrose on the induction of lysosomal hydrolases. In a recent paper (18), we reported that the addition of 88 mM sucrose to the medium of cultured normal human skin fibroblasts as long as 13 days caused a higher increase in the intracellular activities of hydrolases than those reported in the literature with shorter experimental period. In addition, we observed that the lysosomal hydrolases were significantly stimulated in the cultured skin fibroblasts of ICD and the enzymic activities reached the normal range after sucrose loading. Here we report the details of the induction and the normalization of several lysosomal hydrolases in ICD fibroblasts.

MATERIALS AND METHODS

Fibroblast Cell Strains— Cultured skin fibroblasts used in the experiments were derived from normal subjects and two cases of ICD (Nos. 186 and 224). Diagnosis of ICD was made on the basis of both typical clinical features and biochemical characteristics (2-4). The latter is summarized in Table I. Skin biopsies were obtained by punch technique after obtaining informed parental consent; fibroblast cultures were initiated and maintained in Eagle’s minimum essential medium (Nissui Seiyaku Co., Tokyo, Japan), supplemented with 10% fetal bovine serum (Flow Laboratories McLean, VA) as described elsewhere (19). Cells were dissociated with 0.25% trypsin, 0.02% EDTA and subcultured with 1:4 split ratio unless otherwise stated.

All experiments were performed in 10-cm Corning plastic dishes with 10 ml medium.

Sucrose Loading Experiments—Details of the sucrose loading experiments were described in the previous paper (18). Essentially, for the sucrose loading, culture medium supplemented with 3 g/dl (88 mM) of sucrose was not changed for 13 days (intracellular lysosomal hydrolases were measured on the specified days). For the recovery experiment, the fibroblasts were cultured with sucrose for 12 days, and then were trypsinized and subcultured afterwards with the conventional medium without sucrose. Intracellular lysosomal hydrolases were measured on the day of subculture and once every 3 days thereafter.

NH4Cl Loading Experiments—On the 12th day of culture (cultured with 88 mM sucrose in the medium, SUC+; or without, SUC-), after equal number of cells were seeded, old medium was removed and rinsed with fresh serum-free medium (with or without sucrose) three times. Such SUC+ or SUC- group which consisted of two 10-cm dishes with 10 ml of medium was then divided into two groups and incubated with 10 mM NH4Cl (NH4+) or without NH4Cl (NH4-). As a result, intracellular and extracellular hydrolases were assayed after 24 h of incubation in four groups; i.e. SUC NH4+, (control group), SUC-NH4+, SUCNH4+, SUCNH4+ groups. Extracellular enzyme assays were performed with 20 µl of medium and 50 µl of buffered 4-methylumbelliferyl glycoside substrate solution like the intracellular hydrolase assays.

Lysosomal Hydrolase Assays—Cells were rinsed with 0.9% NaCl and detached by rubber policeman. The details of the methods were described in the previous report (20). Protein was measured by the method of Lowry et al. (21).

Reagents—4-Methylumbelliferyl glycosides were purchased from Koch-Light Laboratories (Colnbrook, United Kingdom) and used as artificial substrates for lysosomal hydrolases. Powdered medium of Eagle’s MEM “Nissui” 1 was purchased from Nissui Seiyaku Co., Ltd., (Tokyo, Japan) and filtered in our laboratory.

RESULTS

Induction of Intracellular Lysosomal Hydrolases in Su-
Normalization of I-cell Fibroblasts by Sucrose

**Sucrose Loading Experiments**—ICD fibroblast strains (Nos. 186 and 224) were incubated in the same medium for 13 days with (SUC\(^+\)) or without (SUC\(^-\)) 88 mM sucrose. Five intracellular lysosomal hydrolases, \(\beta\)-galactosidase, \(\beta\)-N-acetylglucosaminidase, \(\alpha\)-mannosidase, \(\alpha\)-fucosidase, and \(\beta\)-glucuronidase, were measured. Data are shown in Fig. 1. In ICD strains, most hydrolase activities of SUC\(^+\) except \(\beta\)-glucuronidase were several times as high as those of SUC\(^-\). The induction ratios of these enzymes were much greater in ICD than in normal fibroblasts in which the ratios were 3.5 at the largest (for \(\alpha\)-mannosidase) (18). Induced enzymic activity levels of ICD well reached the normal activities (indicated as shaded areas in the SUC\(^-\) columns in Fig. 1). Induction of \(\beta\)-glucuronidase was clearly observed in ICD (SUC\(^+\)/SUC\(^-\) = 1.48), whereas no clear change was found in normal fibroblasts (SUC\(^+\)/SUC\(^-\) = 0.95) (18). However, in SUC\(^+\), the activity of \(\beta\)-glucuronidase in ICD fibroblasts did not reach the normal enzymic level.

The same degree of induction was observed in the experiment with heat-inactivated serum (70 °C, 30 min). Two ICD strains demonstrated reproducible induction by sucrose loading between different passages. (Tables II and III; Figs. 1 to 4 showed the data from different experiments).

The changes of intracellular hydrolase activities during the sucrose loading experiment for 13 days are shown in Fig. 2. The effect of sucrose was not found in the first one week. As normal SUC\(^+\) fibroblasts showed somewhat decreased enzymic activities at this period, it is supposed that subculture shock may be a main factor to depress the effects of sucrose (22). In both ICD SUC\(^+\) and normal SUC\(^+\) fibroblasts induction became clear and big after 9th day of incubation.

**Enzymic induction rate of intracellular hydrolase in ICD**

![Diagram](http://example.com/diagram.png)

**Table 1**

| Lysosomal hydrolase activities in lymphocyte and serum from the patients with I-cell disease |
|-----------------------------------------------|
| **Lymphocyte** | **β-Gal** | **β-Hex** | **β-Glc** | **α-Man** | **α-Fuc** |
| Case 1 (No. 186) | 59 | 1517 | 217 | 81 | 80 |
| Case 2 (No. 224) | 31 | 1016 | 187 | 87 | 48 |
| Control (mean ± S.D.) (N = 5) | 77 ± 29.6 | 991 ± 443 | 199 ± 73.9 | 69 ± 26.0 | 48 ± 13.9 |
| Control (range) | 41-118 | 502-1798 | 108-317 | 29-107 | 20-59 |
| **Serum** | | | | | |
| Case 1 (No. 186) | 42 | 16,833 | 2571 | 2250 | 2357 |
| Case 2 (No. 224) | 47 | 675 | 958 | 1052 | 675 |
| Control (mean ± S.D.) (N = 5) | 5.8 ± 3.36 | 880 ± 482 | 57 ± 15.5 | 35 ± 23.7 | 616 ± 96.3 |
| Control (range) | 1.7-12 | 402-1660 | 40-80 | 11-70 | 453-796 |

* 4-Methylumbelliferyl-β-D-galactosidase.
* 4-Methylumbelliferyl-β-D-N-acetylglucosaminidase.
* 4-Methylumbelliferyl-β-D-glucuronidase.
* 4-Methylumbelliferyl-α-mannosidase.
* 4-Methylumbelliferyl-α-fucosidase.

**Enzyme activity is expressed as nanomoles of 4-methylumbelliferone liberated per mg of cell protein per h.**

**Enzyme activity is expressed as nanomoles of 4-methylumbelliferone liberated per ml of serum per h.**

**Fig. 1. Changes of lysosomal hydrolase activities with sucrose loading in ICD fibroblasts.** Equal numbers of cell were subcultured with (SUC\(^+\)) or without (SUC\(^-\)) 88 mM sucrose. After 13 days of incubation, intracellular lysosomal hydrolase activities were determined. ○, No. 186; □, No. 224. Shaded areas in SUC\(^+\) and SUC\(^-\) column show the range of the activities in normal cells with and without sucrose, respectively. Enzyme activity is expressed as nanomoles per mg of cell protein per h. β-Gal, β-D-galactosidase; β-Hex, β-D-N-acetylglucosaminidase; α-Man, α-D-mannosidase; α-Fuc, α-fucosidase; β-Glc, β-D-glucuronidase.
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fibroblasts seemed dose-dependent on sucrose, and the highest rate was observed at 88 mM sucrose concentration (Table II). On the other hand, in normal fibroblasts, dose dependency was not clearly found, and even with lower sucrose concentration (18 mM), the induction rate was nearly the maximum level (SUC'/SUC- = 1.3 to 1.8) (18). Again the induction of β-glucuronidase was not so large as that of other lysosomal hydrolases examined (Table II).

Several saccharides other than sucrose were tested for the loading experiments. Concentration of every saccharide was 88 mM. We observed that sucrose caused the highest effect of inducing intracellular hydrolase activities (9.3 times control for β-galactosidase, 9.22 times for α-mannosidase, and 1.75 times for β-glucuronidase), although maltose, lactose, mannose, and glucose showed relatively good inductive effects (Table III). Thus, it is concluded that except for sucrose, mono- or disaccharides examined were found either poor inducer of hydrolases or inhibitor of cell growth.

Cultured skin fibroblasts (SUC' and SUC- on the 12th day) in 10-cm dishes were trypsinized with split ratio of 1:5 and maintained with the conventional medium (without sucrose) afterwards. The intracellular hydrolase activities were measured on the day of subculture and once every 3 days during the subsequent incubation, and a clear decrease and complete recovery of the activities were found within 10 days after subculture (Fig. 3).

If sucrose-containing medium was changed every 3 days (SUC+-Change+), the induction of intracellular hydrolases was significantly retarded β-galactosidase and α-mannosidase increased less slowly in the SUC+-Change+ than SUC'-. Change-. β-N-Acetylglucosaminidase was not induced with

![Graph](http://www.jbc.org/)

**FIG. 2. Time course of changes of lysosomal hydrolase activities with sucrose loading in ICD and normal fibroblasts (No. 224).** Equal numbers of cell were subcultured into eight dishes with or without 88 mM sucrose. After 2, 6, 9, and 13 days, intracellular lysosomal hydrolase activities were determined. □, ICD cell, control (ICD, SUC-); ■, ICD cell, sucrose loading (ICD, SUC+); ◊, normal cell, control; △, normal cell, sucrose loading. Enzyme activity is expressed as nanomoles per mg of cell protein per h. Abbreviations as in Fig. 1.

**TABLE III**
Effects of different saccharide in medium on the lysosomal hydrolase activities in ICD fibroblast (No. 224)

| Additive | Growth* (µg prot./dish) | β-Gal | α-Man | β-Gal |
|----------|--------------------------|-------|-------|-------|
| None (control) | Good (570) | 2.8 | 1.00 | 3.6 | 1.00 | 18.9 | 1.00 |
| Galactose | Fair (380) | 9.8 | 5.50 | 4.6 | 1.28 | 23.6 | 1.25 |
| Fructose | Good (370) | 24.8 | 8.86 | 3.8 | 1.06 | 22.8 | 1.21 |
| Mannose | Good (432) | 75.7 | 27.0 | 6.4 | 1.78 | 18.2 | 0.96 |
| Glucose | Good (480) | 36.4 | 13.0 | 4.9 | 1.36 | 23.1 | 1.22 |
| Maltose | Good (370) | 34.2 | 12.2 | 6.6 | 1.83 | 19.1 | 1.01 |
| Lactose | Poor (234) | 23.2 | 8.29 | 15.3 | 4.29 | 12.6 | 0.67 |
| Sucrose | Good (522) | 110 | 39.3 | 35.2 | 9.22 | 55.0 | 1.75 |

* Growth of cell was checked under phase contrast microscopy.

**TABLE II**
Effects of sucrose concentration in medium on the lysosomal hydrolase activities in ICD fibroblast (No. 224)

| Conc. of sucrose (mM) | β-Gal | β-Hex | α-Man | α-Fuc | β-Glcr |
|-----------------------|-------|-------|-------|-------|-------|
| 0 (Control)           | 5.5   | 1.00  | 556   | 1.00  |       |
| 4.4                   | 6.2   | 1.13  | 601   | 1.08  |       |
| 8.8                   | 9.4   | 1.71  | 667   | 1.30  |       |
| 18                    | 17.6  | 3.20  | 805   | 1.45  |       |
| 44                    | 71.6  | 13.0  | 1474  | 2.47  |       |
| 88                    | 165   | 30    | 2388  | 4.24  |       |

* Specific activity is expressed as nanomoles per mg of cell protein per h.

* Ratio is expressed in specific enzyme activities at different concentration of sucrose against the value in the control condition (0 mM).

* Ratio in parentheses shows the ratio in normal fibroblast for comparison.
this experimental condition (Fig. 4). In SUC− group, the changes of the intracellular hydrolases were not detected by the change of medium (without sucrose) every 3 days. Therefore, the results of SUC− "Change" group were not indicated in Fig. 4.

**Extracellular Lysosomal Hydrolases Excreted from Normal and ICD Fibroblasts by the Addition of NH4Cl**—Fig. 5 shows the acid α-mannosidase activities excreted from normal and ICD fibroblasts in the sucrose loading and/or the NH4Cl loading experiments. β-N-Acetylglucosaminidase and β-glucuronidase were also assayed in those media. Determination of the enzyme activities in the medium was performed directly without dialysis. The results were very similar to those of acid α-mannosidase.

In the control condition (SUC−·NH4−), the hydrolase activities in the media of ICD fibroblasts was from 3 (β-N-acetylglucosaminidase) to 5 (α-mannosidase) times as high as that of control fibroblasts. The 24 h incubation with 10 mM NH4Cl in the medium of SUC− (SUC−·NH4+) resulted in a clear increase of three hydrolase activities in the medium of normal fibroblasts (SUC−·−NH4+/NH4−= approximately 3). On the contrary, in the medium of ICD SUC−·NH4+ there was no increase or rather slight decrease of the hydrolase activities (SUC−·−NH4+/NH4−= 0.3 to 0.5) (Fig. 5a). Presence of NH4Cl from 1 mM to 100 mM in assay condition caused no inductive nor inhibitory effect (data not shown).

The effect of NH4Cl seemed very much influenced by the presence of sucrose in the medium. Although some increase in hydrolase activities was detected in the control medium of normal fibroblasts after NH4Cl loading (SUC−·−NH4+/NH4−= 3.5), the enhancement of the hydrolase excretion was much more significant in the medium of SUC′·NH4+ group.

In control condition (SUC−·NH4−), α-galactosidase and arylsulfatase A (P-Glucuronidase and P-Acetylglucosaminidase) were also assayed in those media. Determination of the enzyme activities in the medium was performed directly without dialysis. The results were very similar to those of acid α-mannosidase.

The present data demonstrate that the intracellular hydrolases were induced more actively in ICD fibroblasts by 88 mM sucrose loading only when sucrose was already present in the medium (SUC−·−NH4+/NH4−= 1.2 to 2.5) (Fig. 5b).

**DISCUSSION**

The present data demonstrate that the intracellular hydrolases were induced more actively in ICD fibroblasts by 88 mM sucrose loading for 13 days than in normal fibroblasts. In ICD fibroblasts, most hydrolase activities reached their normal ranges (Fig. 1). Besides α-galactosidase and arylsulfatase A...
also reached their normal ranges (data not shown). Probable subculture shock and reversibility of the induction were found in both normal and ICD strains (Figs. 2 and 3). The degree of induction was different between normal and ICD strains. In low concentration of sucrose (18 mm) normal cells reached nearly the maximal induction, whereas ICD cells seemed to respond to the higher concentration of sucrose (up to 88 mm) (Table II). Extracellular hydrolase activities increased linearly in ICD with sucrose loading as in control (data not shown). It seems unlikely that ICD cells with sucrose loading internalize their own secreted hydrolases because it was recognized that a rate of fluid endocytosis was not induced by the addition of 80 mm sucrose in cultured cells (15, 23).

The characteristic inclusion disappeared after sucrose loading when cytoplasm of ICD fibroblasts was investigated by phase contrast (Fig. 6), transmission, and scanning electron microscopies. Subcellular fraction experiments of both ICD and normal fibroblasts revealed that hydrolase activities increased by sucrose loading were detected in latency positive particles, probably packed in intact lysosomes (data not shown). Morphological study on ICD fibroblasts with sucrose loading will be reported elsewhere.

At this time, the precise factor to trigger the hydrolase induction still remains unclear. As several saccharides other than sucrose were found to be poor enzyme inducer (Table I), it seems unlikely that ICD cells with sucrose loading internalize their own secreted hydrolases because it was recognized that a rate of fluid endocytosis was not induced by the addition of 80 mm sucrose in cultured cells (15, 23).

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The changes of β-glucuronidase were apparently different from those of other hydrolases such as a-glucosidase, β-N-acetylgalactosaminidase, a-mannosidase, etc. (Fig. 1 and Table I). However, this does not indicate that β-glucuronidase is an exception among lysosomal hydrolases, since the induction was detected after sucrose loading in ICD SUC" cells (Fig. 1) and bigger extracellular hydrolase accumulation in SUC"NH₄⁺ normal cells (data not shown). Probably, the turnover rate of β-glucuronidase in sucrose loading is higher than others. Warburton and Wynn reported that sucrose loading increased in the rate of degradation (25).

The amount of released hydrolase in serum-free medium in our experiment seems slightly less than that in albumin-supplemented medium used by most investigators (26, 27). The degree of increase in enzymic release by NH4Cl was much bigger in SUC" of normal and ICD cells than in SUC". Again from this experiment, the synthesis of enzyme in both ICD and normal fibroblasts seems to be stimulated by sucrose loading.

Recently, it has been found that ICD fibroblasts are deficient in UDP-N-acetylglucosamine:glycoprotein N-acetylgalactosaminyl phosphotransferase activity and that a pathologically excessive amount of extracellular hydrolases is due to the defect of the signal of hydrolase to react with the transfer proteins (28, 29). For this reason, it appears reasonable that the extracellular hydrolase activities in ICD cells were not increased after NH4Cl loading (SUC"). However, if sucrose stimulates the production of only abnormal enzyme molecules, this theory cannot explain the reason for the increased release of hydrolases from ICD cells in SUC"NH₄⁺ (Fig. 5). This finding seems important. In ICD cells, there may be some residual function to synthesize normal lysosomal hydrolases which can be normally packed in lysosomes (30). Probably the sucrose loading also stimulates this function and produces more receptors and enzymes with normal structure, which could be well shown by the results of NH4Cl loading in Fig. 5b, because released hydrolases by NH4Cl loading were originally to be packed in lysosomes.

Accordingly, sucrose stimulates the production of lysosomal hydrolases and probably of receptor protein, and normalizes the intracellular lysosomes in ICD fibroblasts. Since sucrose normalizes both biochemical and morphological abnormalities in ICD cells, it is hoped that this approach will give an idea to the treatment of ICD.

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