1-Deoxyojirimycin Impairs Oligosaccharide Processing of al-Proteinase Inhibitor and Inhibits Its Secretion in Primary Cultures of Rat Hepatocytes

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1-Deoxyojirimycin was found to inhibit oligosaccharide processing of rat al-proteinase inhibitor. In normal hepatocytes al-proteinase inhibitor was present in the cells as a 49,000 M, high mannose type glycoprotein with oligosaccharide side chains having the composition MansGlcNAc and MansGlcNAc with side chains.

Conversion to complex oligosaccharides resulting in the formation of albumin was unaffected. The oligosaccharides were characterized by their susceptibility to endoglucosaminidase H, incorporation of [3H]galactose, and [3H]fucose and concanavalin A-Sepharose chromatography. It was found that 1-deoxyojirimycin did not completely block oligosaccharide processing, resulting in the formation of al-proteinase inhibitor molecules carrying one or two complex type oligosaccharides. Only these al-proteinase inhibitor molecules processed to the complex type in one or two of their oligosaccharide chains were nearly exclusively secreted. This finding demonstrates the importance of oligosaccharide processing for the secretion of al-proteinase inhibitor.

A series of enzymatic reactions is required for the biosynthesis of glycoproteins containing N-linked oligosaccharides of the complex type (for recent reviews see Refs. 1–4). In the endoplasmic reticulum a transfer of Glc3Man9GlcNAc2-pyrophosphoryldolichol from dolichol derivative to the nascent polypeptide chain occurs. The three terminal glucosyl residues are essential for the transfer of the oligosaccharides to the protein backbone (5).

Inhibitors which block different enzymes in the trimming process have been described recently. 1-Deoxyojirimycin was found to inhibit glucosidases I and II (14). Bromoconduritol B lactone (Bay h 5595) was a generous gift of Bayer Wuppertal, Germany.

We are interested in the secretion mechanisms of glycoproteins. As a model glycoprotein the secretion of al-proteinase inhibitor has been studied in primary cultures of rat hepatocytes. We found that inhibition of glycosylation by tunicamycin inhibited the secretion of al-proteinase inhibitor by 60–70% (17). In further studies we observed that inhibition of mannosidase II by swainsonine led to the formation of incompletely processed glycoprotein. In spite of its effect on the carbohydrate part of al-proteinase inhibitor swainsonine did not impair the secretion of the incompletely processed glycoprotein.

In order to examine the inhibition of glycoprotein processing at an early stage, we studied the effect of 1-deoxyojirimycin on the glycosylation and secretion of al-proteinase inhibitor. In the present paper we show that inhibition of glucose trimming leads to impaired secretion of al-proteinase inhibitor.

MATERIALS AND METHODS

Chemicals—L-[35S]Methionine (>600 Ci/mmol) was purchased from the Radiolabeled Centre, Amersham, and [2-3H]mannose (24 Ci/mmol), [4,5-3H]galactose (52 Ci/mmol), and [6-3H]fucose (84 Ci/mmol), and Protosol were from New England Nuclear. Endoglucosaminidase H from Streptomyces plicatus was obtained from Miles, Frankfurt; tunicamycin was from Calbiochem-Behring, Giessen; protein A-Sepharose CL-4B, activated thiol-Sepharose 4B, concanavalin A-Sepharose, and Sephacryl S-200 were from Pharmacia, Freiburg. Proteinase K was purchased from Merck, Darmstadt. 1-Deoxyojirimycin (Bay h 5555) was a generous gift of Bayer AG, Wuppertal-Ellerfeld.
Preparation of Rat Hepatocyte Monolayers—Suspensions of rat hepatocytes were prepared as previously described by Bischoff et al. (19). After the cells were washed with Krebs-Henseleit buffer, they were suspended in a modified Waymouth medium (20) containing 10% fetal calf serum, 50 units/ml of penicillin, 50 μg/ml of streptomycin, 10−4 M dexamethasone, and 10−3 M insulin. Aliquots of 3 ml of cell pellets were treated with 1% Triton X-100 in immunoprecipitation buffer (Falcon plastic tissue culture dishes). The dishes were incubated at 37 °C in a humid atmosphere of 5% CO2 in air for 3 h. The plates were then washed with Krebs-Henseleit buffer and 3 ml of culture medium (Waymouth medium containing 5% fetal calf serum, penicillin, streptomycin, dexamethasone, and insulin in the same concentrations as mentioned above) were added. Confluent monolayers were formed after an overnight incubation at 37 °C in a humid atmosphere of 5% CO2 in air.

Labeling of Hepatocytes—Modified Waymouth medium without fetal calf serum, bovine serum albumin, and oleic acid was used for the radioactive labeling of the hepatocyte monolayers obtained after overnight incubation. 25 μCi of [35S]methionine were added to 3 ml of methionine-free culture medium for the labeling of proteins. In order to label carbohydrates, 80 μCi of d-[2-3H]glucosamine, 50 μCi of d-[4,5-3H]galactose, or 50 μCi of L-[6-3H]mannose were added to each dish containing about 4 × 106 cells. For the labeling with d-[5-3H] mannose, Waymouth medium containing only 1/5 of the normal glucose concentrations was used. If not otherwise stated, the incubation times were 2.5 h for [35S]methionine and 4 h for the 3H-labeled sugars. After incubation at 37 °C the media were separated from the cells. The cells of each dish were carefully washed with 0.15 M NaCl, 10 mM Tris/HCl, pH 7.6, or 0.14 M NaCl, 5 mM EDTA, 1% Triton X-100 containing 1 mM phenylmethylsulfonyl fluoride and 0.1 mg of kallikrein trypsin inhibitor (kindly provided by Bayer AG, Wuppertal-Elberfeld). After addition of 2.5 μl of a specific antiserum against rat α1-proteinase inhibitor (21) and incubation at 0 °C overnight, the antigen-antibody complexes were bound to 7 mg (dry weight) of protein A-Sepharose and washed 4 times with buffer A and twice with 50 mM sodium phosphate buffer, pH 7.5. Elution was achieved by incubation with 50 mM Tris/HCl, pH 7.6, or 0.14 M NaCl, 5 mM EDTA, 1% Triton X-100 containing 1 mM phenylmethylsulfonyl fluoride and 0.1 mg of kallikrein trypsin inhibitor. After digestion of the complexes with 100 μg/ml of proteinase K in 20 mM Tris/HCl, pH 7.5, 0.02% sodium azide, were used. The void volume marker was bovine serum albumin (66,000 Da). The volume marker used was calculated by using a Packard Tri-Carb liquid scintillation spectrophotometer model 460 C. Treatment of oligosaccharides with α-glucosidase was carried out according to Laemmli (22) and by gel filtration on Sephacryl S-200. The molecular weight standards were bovine serum albumin (66,000), catalase (60,000), ovalbumin (43,000), and alcohol dehydrogenase from yeast (37,000).

RESULTS

1-Deoxynojirymycin was used to inhibit the trimming of the carbohydrate side chains of α1-proteinase inhibitor in primary cultures of rat hepatocytes. Fig. 1 shows the effect of increasing concentrations of 1-deoxynojirymycin on the synthesis and secretion of α1-proteinase inhibitor. As described previously (17, 28), two forms of α1-proteinase inhibitor exist in control hepatocyte cultures: an intracellular 49,000 M, precursor of the high mannose type and an extracellular 54,000 M, glycoprotein of the complex type (Fig. 1, lanes 1 and 2). A small amount of the complex type α1-proteinase inhibitor is also present in the cells. Incubation of hepatocytes with increasing concentrations of 1-deoxynojirymycin ranging from

![Fig. 1. Effect of different concentrations of 1-deoxynojirymycin on the synthesis and secretion of α1-proteinase inhibitor.](http://example.com/fig1.png)
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1.25 to 10 mM leads to the formation of an intracellular form of α1-proteinase inhibitor with an apparent molecular weight of about 51,000 which is higher than that found in control cells. Furthermore, an additional protein band with an apparent molecular weight of about 47,000 is found. The intensity of this band increases with higher 1-deoxynojirimycin concentrations (lanes 3, 5, 7, and 9). At 10 mM 1-deoxynojirimycin (lane 9) a faint band with an even smaller apparent molecular weight (44,000) occurs. The incubation of hepatocytes with 1-deoxynojirimycin prevents the formation of the 54,000 M
complex type α1-proteinase inhibitor normally secreted into the medium. Instead, a form of smaller molecular weight was observed. The secretion of this form was markedly inhibited compared to that of the 54,000 M α1-proteinase inhibitor secreted by control hepatocytes. In none of the experiments with 1-deoxynojirimycin was total protein synthesis inhibited by more than 10-15%.

In order to study the effect of 1-deoxynojirimycin on the size of the oligosaccharide chains of α1-proteinase inhibitor endoglucosaminidase H digests of [3H]mannose-labeled α1-proteinase inhibitor were analyzed on Bio-Gel P-4 columns. It can be seen in Fig. 2A that the majority of the radioactive material from control cells coelutes with the marker ManαGlcNAc. With the exception of radioactivity under the small peak ahead of ManαGlcNAc these oligosaccharides were resistant against treatment with α-glucosidase (Fig. 2B). Thus, in the absence of 1-deoxynojirimycin oligosaccharide chains with 8 and 9 mannose residues are found on α1-proteinase inhibitor. It is documented in Fig. 2C that the majority of oligosaccharides of α1-proteinase inhibitor which are synthesized in the presence of 1-deoxynojirimycin elute under three peaks ahead of the reference ManαGlcNAc, the largest coeluting with GlcαManαGlcNAc. Their elution positions are shifted after treatment with α-glucosidase to posi-

![Figure 2](http://www.jbc.org/)

**Fig. 2.** Chromatography on Bio-Gel P-4 columns of oligosaccharides derived from α1-proteinase inhibitor formed in the absence or presence of 1-deoxynojirimycin before or after treatment with rat liver glucosidase. [3H]Mannose-labeled oligosaccharides derived from α1-proteinase inhibitor by treatment with endoglucosaminidase H formed in the absence (A and B) or presence (C and D) of 1-deoxynojirimycin were chromatographed directly (A and C) on columns of Bio-Gel P-4 (~400 mesh, 1 x 150 cm) or after incubation with rat liver glucosidase (B and D) for 120 min. The reaction was stopped by boiling the mixture for 3 min, and [3H]-labeled standards (1, GlcαManαGlcNAc; 2, ManαGlcNAc) were added. V0, elution position of bovine serum albumin. Fraction volume was 850 μL.

![Figure 3](http://www.jbc.org/)

**Fig. 3.** Endoglucosaminidase H treatment of α1-proteinase inhibitor from control and 1-deoxynojirimycin-treated hepatocytes. Rat hepatocytes were preincubated without (lanes 1-4) or with (lanes 5-8) 5 mM 1-deoxynojirimycin for 1 h followed by labeling with [35S]methionine (25 μCi/dish) for 2.5 h. α1-Proteinase inhibitor was immunoprecipitated from control cells (lanes 3 and 4) and their respective media (lanes 1 and 2), from 1-deoxynojirimycin-treated cells (lanes 7 and 8) and their respective media (lanes 5 and 6) and incubated without (lanes 1, 3, 5, and 7) or with (lanes 2, 4, 6, and 8) 5 milliunits of endoglucosaminidase H at 37°C for 16 h as described under "Materials and Methods." Lane 9 shows the intracellular form of α1-proteinase inhibitor obtained after tunicamycin treatment of hepatocytes. Tunicamycin was given to the culture medium at a concentration of 3 μg/ml. After 1 h of incubation the medium was removed and fresh medium containing 25 μCi of [35S]methionine and tunicamycin at a final concentration of 3 μg/ml was added. After a labeling period of 3 h α1-proteinase inhibitor was immunoprecipitated from the cells. Molecular weight markers were the same as those given in the legend to Fig. 1.
tions which correspond to a lower molecular weight, mainly Man$_2$GlcNAc.

To further characterize the $\alpha_1$-proteinase inhibitor species synthesized and secreted in the presence of 5 mM 1-deoxynojirimycin, digestions with endoglucoasaminidase H have been carried out. Whereas the 54,000 molecular weight form of $\alpha_1$-proteinase inhibitor found in the medium of control cells was resistant to the action of endoglucosaminidase H (Fig. 3, lanes 1 and 2), the 49,000 intracellular form was found to be sensitive to endoglucosaminidase H (Fig. 3, lanes 3 and 4). The weak band above the 54,000 $M_r$, $\alpha_1$-proteinase inhibitor (Fig. 3, lanes 1 and 2) is an artefact, which rarely occurs during immunoprecipitation and is not related to $\alpha_1$-proteinase inhibitor.

When $\alpha_1$-proteinase inhibitor was immunoprecipitated from the medium of 1-deoxynojirimycin treated hepatocytes, 2 bands corresponding to apparent molecular weights of about 52,000 and 48,000 were observed (lane 5). Incubation with endoglucosaminidase H led to the formation of two major bands with apparent molecular weights of 49,000 and 46,000 and a minor one with an apparent molecular weight of 43,000 (lane 6). The intracellular $\alpha_1$-proteinase inhibitor from 1-deoxynojirimycin-treated hepatocytes could be deglycosylated by endoglucosaminidase H, resulting in a protein with an apparent molecular weight of about 43,000 (lanes 7 and 8).

For comparison lane 9 shows $\alpha_1$-proteinase inhibitor isolated from tunicamycin-treated hepatocytes. $\alpha_1$-Proteinase inhibitor cleaved by endoglucosaminidase H exhibits a slightly higher apparent molecular weight than the unglycosylated form obtained after tunicamycin treatment ($M_r = 41,000$). This difference is very likely due to the fact that endoglucosaminidase H leaves the first GlcNAc molecule of each oligosaccharide chain attached to asparagine.

From experiments where glycosylation of rat $\alpha_1$-proteinase inhibitor was incompletely inhibited by low doses of tunicamycin, we have concluded that rat $\alpha_1$-proteinase inhibitor carries three oligosaccharide chains (17). This agrees with the conclusions of Carlson and Stenflo (29) drawn from experiments where the high mannose type $\alpha_1$-proteinase inhibitor was incompletely digested with endoglucosaminidase H. Furthermore, the carbohydrate composition of rat serum $\alpha_1$-proteinase inhibitor (30) is in accordance with the existence.
of three oligosaccharide chains.

As shown in Fig. 3 (lanes 7 and 8) the two intracellular forms of α1-proteinase inhibitor found in 1-deoxynojirimycin-treated hepatocytes are both susceptible to endoglucoasaminidase H. Therefore, we conclude that the two forms are different with respect to their number of oligosaccharide chains (3 chains for the upper, and 2 chains for the lower band) and not to their carbohydrate type. This might be due to an inhibitory effect of 1-deoxynojirimycin on the glycosylation of newly synthesized glycoproteins. In the medium of 1-deoxynojirimycin-treated hepatocytes also two different forms of α1-proteinase inhibitor of slightly higher apparent molecular weights than the intracellular forms are present (Fig. 3, lane 5). From the fact that the majority of the medium forms of α1-proteinase inhibitor isolated from 1-deoxynojirimycin-treated cells cannot be completely deglycosylated by endoglucoasaminidase H, we conclude that the secreted forms of α1-proteinase inhibitor contain oligosaccharides of both the high mannose and the complex type. A minute amount of the secreted α1-proteinase inhibitor contains only high mannose type oligosaccharides (see faint band corresponding to an apparent molecular weight of 43,000). The results show that the oligosaccharide trimming is not completely inhibited by 1-deoxynojirimycin. They further suggest that the α1-proteinase inhibitor molecules which have one or two complex type oligosaccharide chains are preferentially secreted.

In order to characterize the oligosaccharide side chains of α1-proteinase inhibitor secreted from 1-deoxynojirimycin-treated hepatocytes, the carbohydrate part of α1-proteinase inhibitor was labeled with [3H]mannose and analyzed by affinity chromatography on concanavalin A-Sepharose as described by Reitman et al. (31). Fig. 4A shows that the [3H]mannose-labeled glycopeptides obtained after proteinase K digestion of the sodium dodecyl sulfate-denatured α1-proteinase inhibitor from the medium of control cells are found essentially in the flow-through fractions and the 10 mM α-methylglucoside eluate. The glycopeptides of α1-proteinase inhibitor secreted by 1-deoxynojirimycin-treated hepatocytes were found partially in the flow-through fractions and in the 10 mM α-methylglucoside eluate; the largest amount, however, was found in the 500 mM α-methylmannoside eluate. The results of the concanavalin A-Sepharose chromatography suggest that control cells secrete α1-proteinase inhibitor with mainly bi- and some probably tri- or tetra-antennary oligosaccharide chains. 1-Deoxynojirimycin-treated cells, on the other hand, secrete α1-proteinase inhibitor containing complex type (flow-through and 10 mM α-methylglucoside eluate) and high mannose type oligosaccharides (500 mM α-methylmannoside eluate). To further demonstrate the existence of complex type oligosaccharides in α1-proteinase inhibitor secreted from 1-deoxynojirimycin-treated hepatocytes, cells were labeled with [3H]galactose or [3H]fucose. The [3H]galactose- or [3H]fucose-labeled glycopeptides were subjected to concanavalin A-Sepharose affinity chromatography (Fig. 4B). The elution profiles show that the [3H]galactose or [3H]fucose-labeled oligosaccharides are of the complex type.

To study the inhibitory effect of 1-deoxynojirimycin on the secretion of α1-proteinase inhibitor (already presented in Fig. 1) in greater detail, pulse-chase experiments were carried out. For comparison, albumin, an unglycosylated secretory protein, has been examined. Hepatocytes were pulse-labeled with [35S]methionine for 10 min followed by a chase with unlabeled methionine. When α1-proteinase inhibitor (Fig. 5A) and albumin (Fig. 5C) were immunoprecipitated from the cells and from the medium at different times ranging from 10 to 180 min, a continuous decrease of radioactivity in the cells and an increase of radioactivity in the medium was found. When the same pulse-chase experiments were carried out under conditions, where oligosaccharide trimming was blocked by 1-deoxynojirimycin, it was found that the secretion of α1-proteinase inhibitor (Fig. 5B) was markedly inhibited, whereas the secretion of albumin (Fig. 5D) was not affected.

In Table 1 the data of the pulse-chase experiments (Fig. 5) are quantitated and show that 1-deoxynojirimycin inhibits the secretion of α1-proteinase inhibitor but does not affect albumin secretion.

### Table 1

**Effect of 1-deoxynojirimycin on the secretion of α1-proteinase inhibitor and rat serum albumin**

| Time after chase | α1-Proteinase inhibitor | Rat serum albumin |
|------------------|-------------------------|------------------|
| min              | Control | 1-Deoxynojirimycin | Control | 1-Deoxynojirimycin |
| 10               | 0       | 0                 | 0       | 0                 |
| 30               | 0.05    | 0.02              | 0.17    | 0.15              |
| 60               | 0.46    | 0.24              | 0.75    | 0.75              |
| 90               | 0.69    | 0.38              | 0.85    | 0.90              |
| 120              | 0.81    | 0.48              | 0.94    | 0.94              |

The radioactive bands containing [35S]methionine-labeled α1-proteinase inhibitor and rat serum albumin from the pulse-chase experiments presented in Fig. 5 were cut from the gels and their radioactivity was measured. For each protein the ratio of extracellular to intracellular radioactivity is given for the various times after chase.
The amount of α₁-proteinase inhibitor secreted during 24 h by cultured rat hepatocytes was determined by rocket immuno-electrophoresis. Normal rat hepatocytes secreted 4.39 µg of α₁-proteinase inhibitor/mg of cellular protein. In the presence of 5 mM 1-deoxynojirimycin only 2.15 µg of α₁-proteinase inhibitor/mg of cellular protein/24 h was secreted.

**DISCUSSION**

1-Deoxynojirimycin has been found to inhibit glucosidase activities (32, 33), including the glucosidases involved in the processing of Glc₃Man₂GlcNAc₂ oligosaccharides from *Streptomyces cerevisiae* (14). In this paper we report that incubation of hepatocytes with 1-deoxynojirimycin results in the formation of an intracellular α₁-proteinase inhibitor form (apparent Mr 51,000) larger than that found in normal cells (apparent Mr 49,000). The analysis of the oligosaccharides obtained after endogluocosaminidase H digestion showed that α₁-proteinase inhibitor synthesized in the absence of 1-deoxynojirimycin carries high mannose oligosaccharides containing 9 and 8 mannose residues, the predominant species being Man₉GlcNAc. With the exception of a small peak ahead of the marker Man₈GlcNAc (see "Results") oligosaccharides are insensitive against treatment with α₁-glucosidase. The elution profile obtained upon analysis of oligosaccharides which have been trimmed with respect to their mannose and, in addition, some glucose-containing oligosaccharides is consistent with the hypothesis that an intracellular α₁-proteinase inhibitor form (apparent Mr 49,000) is present in the same ratio intra- and extracellularly. Analysis of the carbohydrate part of α₁-proteinase inhibitor secreted by Reitman et al. (31). They studied a lectin-resistant mouse lymphoma cell line which showed a nearly complete lack (<0.3% of parent) of glucosidase II, but still made complex type oligosaccharides in an amount of 25% of that found in the parent cells.

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