Impaired Intestinal Sugar Transport in Cirrhotic Rats: Correction by Low Doses of Insulin-like Growth Factor I

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Background & Aims: Malnutrition is a complication of liver cirrhosis accompanied by reduced insulin-like growth factor I (IGF-I) availability. The aim of this study was to analyze the effect of IGF-I on intestinal D-galactose absorption in cirrhotic rats. Methods: IGF-I (2 μg·100 g body wt⁻¹·day⁻¹) or saline were given for 14 days to rats in whom cirrhosis was induced with CCl₄. Galactose transport and sodium–glucose/galactose–ligand transporter 1 (SGLT-1) expression were assessed in jejunal rings and in brush border membrane vesicles (BBMVs). Results: Compared with that in controls, galactose transport in everted jejunal rings was significantly reduced in cirrhotic rats but showed normal values after IGF-I treatment. The kinetic study of D-galactose uptake by BBMVs showed decreased maximal velocity (Vmax) and diminished transporter affinity in cirrhotic rats. These kinetic parameters reverted to normal after IGF-I treatment. Microvilli were significantly elongated in cirrhotic rats but of normal size in the IGF-I–treated group. The expression of SGLT-1 on BBMVs (Western blot) and on the luminal membrane of enterocytes (immunohistochemistry) was not reduced in cirrhotic animals compared with controls or IGF-treated cirrhotic rats. Conclusions: Intestinal sugar transport is disturbed in experimental cirrhosis, and this alteration is corrected by IGF-I.

Malnutrition frequently accompanies liver cirrhosis.¹⁻⁶ In advanced disease, this complication determines poor survival and negatively influences the outcome of liver transplantation.⁵⁻⁷ Except for the substitution of the diseased liver, no treatment that can improve nutritional status in cirrhotic patients is yet available.

Insulin-like growth factor I (IGF-I) is an important anabolic hormone with pleiotropic actions; IGF-I has also been shown to stimulate gastrointestinal growth and function.⁸⁻⁹ The digestive tract is one of the systems where IGF-I receptors are densely expressed.¹⁰⁻¹³ Although IGF-I is produced in many organs, the liver is the main site for biosynthesis of circulating IGF-I.¹⁴⁻¹⁵ Bioavailability of IGF-I depends on its serum levels and also on its binding to different forms of IGF-binding proteins.¹⁶⁻¹⁷ Reduced bioavailability of this hormone has been shown in advanced cirrhosis,¹⁴⁻¹⁵ and deficiency of IGF-I has been proposed as one of the factors that can affect nutritional status in cirrhotic patients.¹⁸ In a previous study, we showed that administration of IGF-I, at low doses, improved different nutritional parameters in rats with carbon tetrachloride–induced cirrhosis.¹⁸ In this study, we used low doses of IGF-I to avoid the induction of hypoglycemia, an effect that could hamper the anabolic potential of the hormone.

Impaired digestion and/or absorption of nutrients has been considered one of the possible mechanisms involved in the nutritional disturbance of cirrhosis.¹⁻⁶ Carbohydrates are the main constituents of human diet and the main energy supply; to be absorbed, they need to be broken down to monosaccharides. Uptake of glucose and galactose by enterocytes is mediated by a sodium-glucose/galactose cotransporter protein (SGLT-1)²⁰ located at the brush border membrane. This cotransporter requires energy derived from the electrical and sodium gradient across the luminal membrane.²⁰⁻²³ Sugar accumulated in the enterocyte moves to the capillary blood via the facilitated transporter isoform facilitative glucose transporter 2 of the basolateral membrane.²⁰⁻²⁵ In the present study, we investigated whether intestinal sugar absorption is impaired in experimental cirrhosis and whether IGF-I administration could influence sugar absorption in this condition.

Materials and Methods

Animals and Experimental Design

All experimental procedures were performed in conformity with The Guiding Principles for Research Involving Animals.²⁴

Abbreviations used in this paper: BBMV, brush border membrane vesicle; IGF-I, insulin-like growth factor I; Kᵣ, affinity constant; SDS, sodium dodecyl sulfate; SGLT-1, sodium–glucose/galactose–ligand transporter 1; TBS-T, Tris-buffered saline with 0.1% Tween 20; Vmax, maximal velocity.

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Liver cirrhosis was induced by CCl4 inhalation over 11 weeks in male Wistar rats weighing ~160–170 g. Phenobarbital (Luminal; Bayer, Leverkusen, Germany) was added to drinking water (400 mg/L) beginning 1 week before the first CCl4 exposure.

Four groups of age-matched rats were included in this study. In two groups, liver cirrhosis was induced as mentioned; 1 week after stopping CCl4 administration (day 0 of the experimental period), animals were treated with either saline (group CI) or IGF-I subcutaneously (2 µg·100 g body wt·day−1) (group CI + IGF) for 2 weeks. Two other groups were used as healthy controls; one of them (CO group) received saline, and the other was treated with IGF-I (CO + IGF) at the same doses as CI + IGF over the 2 weeks.

On day 0 of the experimental period, blood (6 mL) from retroocclusal plexus was collected from 10 controls (CO) and 20 cirrhotic rats. At the end of the experimental period (day 15), animals were killed, blood samples were taken, and jejenum, liver, and spleen were dissected and weighed. Liver samples were taken for histological examination, and samples of jejunum were collected for functional and histological studies.

In 32 rats (8 from each group), intestinal absorption of D-galactose was assessed by using everted jejunal rings. In addition, kinetic analysis of the sugar transport was performed in 27-gauge needle. The specific activity of the brush boundary marker enzyme sucrase (EC 3.2.1.48) was determined as described by Crane and Mandelstan. 

**Biochemical Determinations**

Serum levels of albumin, total proteins, glucose, cholesterol, bilirubin, alkaline phosphatase, and aspartate and alanine transaminases (AST and ALT) were determined by routine laboratory methods using a Hitachi 747 autoanalyzer (Boehringer-Mannheim, Germany). Insulin was measured by radioimmunoassay using a commercial kit (Insik-5; Sorin Biomedical, Saluggia, Italy).

**Uptake of D-Galactose by Everted Jejunal Rings**

The incorporation of labeled D-galactose into everted jejunal rings was determined as described by Crane and Mandelstan. 

Briefly, the procedure involved the following steps. After animals were killed, a portion (20 cm) of the jejunum was quickly excised and rinsed with an ice-cold saline solution containing 140 mmol/L NaCl, 10 mmol/L KHCO3, 0.4 mmol/L K2HPO4, 2.4 mmol/L KH2PO4, 1.2 mmol/L CaCl2, and 1.2 mmol/L MgCl2 (pH 7.4). Three pieces of intestine, forming closed and everted intestinal rings and weighing ~50 mg each, were incubated for 30 minutes at 37°C and gassed continuously (95%O2/5%CO2) in the mentioned buffer containing 2.0 mmol/L D-galactose, 0.1 µCi/10 mL of radioactive D-galactose (sp act, 50–60 mCi/mmol; Amersham Radiochemical Center, London, England), and 1 µCi/10 mL of tritium-labeled polyethylene glycol ([1H2]PEG-4000; Merck, Darmstadt, Germany). [1H2]PEG-4000 was used as a marker for extracellular water. At the end of the incubation, tissues were washed in ice-cold saline solution, blotted carefully to remove excess moisture, weighed wet, and extracted by shaking for 24 hours in 100 mmol/L HNO3 (0–4°C). The tissue was then dried at 110°C for at least 48 hours and weighed. Radioactivity was determined by a liquid scintillation counting in a Wallac 1409 (Pharmacia, Turku, Finland). Values are expressed in micromoles of D-galactose per milliliter of intracellular water.

**Preparation of BBMVs and Uptake Kinetics of D-Galactose**

BBMVs were prepared using an Mg2+-precipitation method with some modifications. 

The study of the kinetics of D-galactose uptake by BBMVs was performed at 0–4°C. The everted jejunum was placed in 2 mmol/L Tris-HCl (pH 7.4) containing 100 mmol/L mannitol and stirred for 3 minutes (Vibro-mixer, E-1; Sorvall, Dupont, Wilmington, DE), and the scraped jejunal mucosa was removed.

The mucosal suspension, mixed with 10 mmol/L MgCl2, was centrifuged three times at 10,000g (for 15 minutes, obtaining supernatant), 26,000g (for 30 minutes, taking the pellet), and 26,000g (for 30 minutes). This final pellet was resuspended in the desired volume of 300 mmol/L mannitol, 0.1 mmol/L MgSO4, and 10 mmol/L Tris-HEPES buffer (pH 7.4; load solution) to give a final protein concentration of 8–10 mg/mL. Isolated membranes were circled by using a 27-gauge needle. The specific activity of the brush border marker enzyme sucrase (EC 3.2.1.48) was determined in BBM suspension, and its enrichment was found to be 10.5 ± 1–fold greater than that of the initial mucosal suspension.

The protein content of the BBMVs was determined according to the method of Bradford.

**Histology, Electron Microscopy, and Immunohistochemistry**

Conventional histological techniques for optical and electron microscopy were used to examine samples of liver and jejunum. In both studies, four fields from each animal were evaluated twice by two different observers, and the length of microvilli and villi was recorded. The arithmetical mean of the two scores was taken as the final measurement.
Immunohistochemical staining of SGLT-1 in paraffin sections (4 μm) was performed with modifications using an avidin-biotin peroxidase technique as described by Shu et al.33 SGLT-1 epitopes masked by fixation were revealed by antigen retrieval by heating the sections in citric buffer (pH 6) in a 700-W microwave oven for 40 minutes. Polyclonal anti-SGLT-1 serum (diluted 1:1000) was kindly donated by Prof. E. M. Wright (Los Angeles, CA).22 Negative controls were performed by omission of any of the layers of the immunohistochemical protocol or omission of antigen retrieval procedure and also by using nonimmune mouse serum as the first layer. The intensity of SGLT-1 staining was measured using a the Visilog 4.1.5 Image Analysis System (Noesis S.A., Vélizy, France). Images were captured with the help of a JVC CCD Camera (TK-970E; Imaging Research, Quebec, Canada) and processed by a Magi/RGB Matrox digital System (Matrox Electronic System, Quebec, Canada). The computer calculated the gray intensity, assuming 0 arbitrary units of color intensity as white and 255 as black. In each slide, 25 similar brush border fields were randomly measured, and the arithmetical mean was calculated.

Western Blot Analysis of BBMVs

BBMVs (50 μg) were solubilized in a buffer containing 5% sodium dodecyl sulfate (SDS) and separated on a 10% SDS-polyacrylamide. Proteins were transferred electrophoretically to nitrocellulose filters for 2 hours at a constant current of 370 mA/cm², and nonspecific sites were blocked by incubation for 2 hours at room temperature with Tris-buffered saline containing 0.1% Tween 20 (TBS-T) and 5% fat-free milk. The filters were then incubated with polyclonal anti-SGLT-1 antibody (1:1000) for 16 hours at 4°C. Afterwards, filters were washed (2 × 15 minutes) with TBS-T, incubated with an ass anti-rabbit IgG biotinylated antibody (1:500) (Amersham International, Buckinghamshire, England) and processed by a Magi/RGB Matrox digital System (Matrox Electronic System, Quebec, Canada). The computer calculated the gray intensity, assuming 0 arbitrary units of color intensity as white and 255 as black. In each slide, 25 similar brush border fields were randomly measured, and the arithmetical mean was calculated.

Statistical Analysis

Data are expressed as means ± SEM. To assess the homogeneity among groups, the Kruskall–Wallis test was used, followed by multiple post hoc comparisons using Mann–Whitney U tests with Bonferroni adjustment. Any P value of <0.05 was considered to be statistically significant. Calculations were performed using the SPSSW (SPSS Inc., Chicago, IL) in program version 6.0. The Sigma Plot Program (version 3.02 for PC) was used to process data of the kinetics of D-galactose uptake by BBMVs.

Table 1. Biochemical Data in Healthy Control Rats and in Rats Exposed to CCl₄

<table>
<thead>
<tr>
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<th>Healthy control rats (n = 10)</th>
<th>Rats exposed to CCl₄ (n = 20)</th>
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<tbody>
<tr>
<td>AST (IU/L)</td>
<td>37 ± 3.3</td>
<td>290 ± 40*</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>19 ± 2</td>
<td>273.5 ± 49.4a</td>
</tr>
<tr>
<td>Glycemia (mg/dL)</td>
<td>192 ± 7</td>
<td>116 ± 5*</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.4 ± 0.03</td>
<td>2.9 ± 0.22b</td>
</tr>
<tr>
<td>Total proteins (g/dL)</td>
<td>6.5 ± 0.08</td>
<td>6.0 ± 0.17b</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>82 ± 4.1</td>
<td>115 ± 4.9*</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>283 ± 17</td>
<td>703 ± 140*</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>0.40 ± 0.04</td>
<td>1.21 ± 0.33b</td>
</tr>
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</table>

NOTE. In the CCl₄ group, values correspond to day 0 of the study (7 days after completion of the 11-week protocol for the induction of cirrhosis).
*P < 0.001, controls vs. CCl₄-exposed animals.
**P < 0.05, controls vs. CCl₄-exposed animals.

Results

One week after completion of the 11 weeks of induction of cirrhosis (day 0 of the experimental period), rats that had received CCl₄ showed altered biochemical values indicating the presence of liver damage and diminished hepatic biosynthetic functions (Table 1). Histological examination at the end of the study (day 15 of the experimental period) confirmed the presence of cirrhosis in all animals that had received CCl₄ (CI and CI + IGF groups). At that point, glucose levels were significantly reduced in CI rats (161.5 ± 6.4 mg/dL) compared with both the CO (199.4 ± 7.5 mg/dL) and CI + IGF (189.7 ± 10.9 mg/dL) groups (P < 0.005 for both comparisons). At the end of the study, body weight had decreased and the weight of the spleen was greater in the two groups of cirrhotic animals compared with controls (Table 2). Cirrhotic animals showed mild or absent ascites.

Absorption of D-Galactose by Everted Jejunal Rings

The study of D-galactose absorption by everted jejunal rings showed a significant decrease in intestinal sugar absorption (1.55 ± 0.025 μmol/mL intracellular water) in CI rats compared with CO (2.34 ± 0.04; P < 0.001), whereas CI + IGF-I showed values similar to those in controls and significantly higher values than in CI animals (2.18 ± 0.02; P = NS vs. CO and P < 0.001 vs. CI). Healthy rats treated with IGF-I (CO + IGF-I) showed values of D-galactose incorporation (2.24 ± 0.03) similar to those found in untreated controls (CO). No changes in compartmental water levels were observed among the different groups of animals (CO, 0.76 ± 0.01; CO + IGF, 0.76 ± 0.01; CI, 0.74 ± 0.02; CI + IGF, 0.75 ± 0.01 mL intracellular water/g wet
Table 2. Body Weight and Weight of Liver, Spleen, and Testis in Each Group of Animals

<table>
<thead>
<tr>
<th></th>
<th>CO (n = 20)</th>
<th>CO + IGF (n = 8)</th>
<th>CI (n = 20)</th>
<th>CI + IGF (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt (g)</td>
<td>545 ± 14</td>
<td>539 ± 18</td>
<td>460 ± 12*</td>
<td>458 ± 9*</td>
</tr>
<tr>
<td>Jejunum</td>
<td>0.59 ± 0.02</td>
<td>0.61 ± 0.03</td>
<td>0.61 ± 0.02</td>
<td>0.65 ± 0.03</td>
</tr>
<tr>
<td>Liver</td>
<td>2.99 ± 0.07</td>
<td>2.83 ± 0.05</td>
<td>3.59 ± 0.15</td>
<td>3.50 ± 0.18</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.15 ± 0.01</td>
<td>0.15 ± 0.00</td>
<td>0.33 ± 0.04*</td>
<td>0.30 ± 0.03*</td>
</tr>
</tbody>
</table>

NOTE. Weight of jejunum, liver, and spleen measured per 100 g body weight.

*P < 0.001 vs. both control groups.

D-Galactose Uptake by BBMVs

Figure 1 shows the uptake of galactose by BBMVs in the presence or absence of a sodium gradient. In the absence of a sodium gradient, the incorporation of sugar to BBMVs was negligible, but in the presence of a sodium gradient, sugar uptake was very rapid, reaching 1770 ± 51, 1668 ± 39, and 756 ± 28 pmol/mg protein at 3 seconds in CO, CI + IGF, and CI rats, respectively. Maximal incorporation of galactose to BBMVs was at 5 seconds. At that point, galactose uptake in controls was 18-fold higher than at minute 10 (when an equilibrium was reached between galactose concentrations inside and outside vesicles). In the presence of a sodium gradient, galactose uptake by BBMVs at 5 seconds was significantly reduced in CI animals compared with CO (P < 0.001). In contrast, BBMVs from CI + IGF rats showed values of D-galactose uptake similar to those in CO and significantly higher than in CI (P < 0.001; Figure 1).

To analyze the kinetics of D-galactose uptake by BBMVs, vesicles were incubated in the presence of increasing concentrations of substrate, from 0.05 to 10 mmol/L, for 3 seconds. Data are shown in Figure 2, in which each point represents the mean of three determinations for a given concentration of the substrate, using a pool of BBMVs from the different experimental groups (n = 12 for each group). The kinetic constants (Kt and Vmax) of D-galactose uptake by BBMVs showed significant alterations in CI rats compared with CO animals (Kt = 0.98 ± 0.02 mmol/L; Vmax = 2447 ± 40.2 pmol·mg protein⁻¹·s⁻¹ in CI rats; Kt = 0.66 ± 0.01 and Vmax = 3746 ± 26.3 in CO rats; P < 0.05 and P < 0.001, respectively). Interestingly, kinetic constants in CI + IGF rats (Kt = 0.73 ± 0.01 and Vmax = 3664 ± 33.6) were not different from those found in CO animals (P = NS) and were significantly improved compared with CI rats (P < 0.05, Kt; P < 0.001, Vmax). Thus, our results show diminished Vmax and reduced transporter affinity for the substrate in BBMVs from CI animals and a return to normal of these constants in CI + IGF rats.
SGLT-1 Expression at the Brush Border

To analyze possible changes in the expression of the transporter protein SGLT-1 located at the brush border membrane, we performed immunohistochemical studies in sections of jejunum. Unexpectedly, we found increased immunostaining of SGLT-1 at the brush border of jejunal enterocytes in CI rats (209 ± 2 arbitrary units of color intensity) compared with CO (160 ± 2; \(P < 0.01\)) (Figure 3). In CI + IGF rats, the intensity of SGLT-1 staining was intermediate between CO and CI animals (180 ± 5 arbitrary units of color intensity; \(P < 0.05\), labeled CO; \(P < 0.01\), labeled CI group).

To determine the amount of SGLT-1 protein anchored at the membrane of microvilli, we performed Western blot analysis in BBMVs using the same anti–SGLT-1 polyclonal antibody that was used in the immunohistochemical studies. As shown in Figure 4, the amounts of SGLT-1 protein present in BBMVs were similar between the three groups of animals.

Morphological Changes in Jejunum

Electron-microscopic studies of the jejunal mucosa (Figure 5) showed that the length of microvilli was significantly greater in CI rats than in CO rats (2.87 ± 0.33 vs. 1.74 ± 0.08 μm; \(P < 0.001\)), whereas in CI + IGF animals the length of microvilli (1.92 ± 0.33 μm) was not different from that in controls. Cytoskeletal filaments at the base of microvilli form a more dense framework in CI + IGF and in control animals than in CI rats. A slight, although significant, elongation of villi was also apparent by optic microscopy in CI rats compared with CO rats (1.037 ± 0.012 vs. 0.847 ± 0.01 mm; \(P < 0.001\)). Villi were of normal length in CI + IGF animals (0.836 ± 0.009 mm; \(P < 0.001\) vs. CI group).

Discussion

It has been suggested that, among other factors, altered digestion and absorption of nutrients might play a role in the malnutrition that occurs in liver cirrhosis. However, malabsorption of a particular nutrient as a result of the failure of a specific intestinal transport system has not been described in cirrhotic patients.

![Figure 3. Immunohistochemistry for SGLT-1 in histological sections of jejunum. Increased staining for SGLT-1 can be seen in the untreated cirrhotic rat. (A) Healthy control, (B) untreated cirrhotic rat, (C) IGF-1–treated cirrhotic rat.](image1)

![Figure 4. Western blot for SGLT-1 in BBMVs in the three groups of rats. The apparent molecular masses are indicated at left. Scanning of the bands showed similar optical density values in the three groups of animals (CO, 0.305; CI, 0.343; CI + IGF, 0.297).](image2)
The present report shows that sugar absorption is impaired in nonadvanced experimentally induced cirrhosis. This functional defect is accompanied by structural changes in the intestinal mucosa, the most striking of which is the elongation of microvilli. Although a diversity of factors, including portal hypertension and altered liver function, might participate in the genesis of these changes, our results indicate that they may be reversed by IGF-I treatment.

IGF-I has been shown to stimulate DNA and protein synthesis in intestinal epithelial cell lines,\(^{12}\) and accumulating evidence indicates that this hormone exerts important trophic activities on the intestine,\(^8,^{11,34}\) acting as autocrine and paracrine mediators of gastrointestinal metabolism and growth.\(^{10,12,35,36}\) IGF-I bioavailability, which depends on the levels of both IGF-I and its IGF-binding proteins, has been reported to be reduced in liver cirrhosis.\(^{14,15}\) In the present work, administration of low doses of IGF-I to cirrhotic rats enhanced galactose absorption and reverted the structural changes observed in the intestinal mucosa of cirrhotic rats. As previously noted,\(^{18}\) these low doses do not significantly increase circulating levels of IGF-I in rats with early cirrhosis but induce significant changes in the pattern of IGF binding proteins that are critical modulators of the biological actions of IGF-I.\(^{17}\)

In cirrhotic rats, we have shown impaired sugar transport and correction of the defect by IGF-I using both everted jejunal rings and BBMVs. The latter technique revealed decreased \(V_{\text{max}}\) and reduced affinity for the ligand in CI animals. Notably, IGF-I treatment was able to restore these kinetic parameters to normal values. The observation that, despite differences in galactose transport, the amounts of SGLT-1 per milligram of protein in BBMVs were similar in CO, CI, and CI + IGF rats was of interest (Figure 3). On the other hand, hyperexpression of SGLT-1 was found at the brush border of enterocytes in histological sections from CI rats (Figure 3). Although this finding seems paradoxical, comparison of the electron micrographs of the enterocyte brush border (Figure 5) and the immunohistochemistry for SGLT-1 (Figure 3) allow the postulation to be made that the strong SGLT-1 immunostaining found in CI animals might be related to increased microvillus length. However, a higher abundance of the transporter at the brush border of cirrhotic animals cannot be excluded. In fact, modifications in the expression of SGLT-1 at the enterocyte brush border have been described in other conditions, such as in hypoglycemia or hyperglycemia.\(^{37,39}\)

In our study, microvilli were found to be significantly elongated in CI rats but exhibited normal length in IGF-1–treated animals. IGF-I has been shown to induce

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**Figure 5.** (A–C) Electron micrographs showing microvilli from jejunal enterocytes in the three experimental groups referred to in Figure 3 (original magnification 16,000×). A marked and significant elongation of microvilli was observed in untreated cirrhotic rats, but microvilli of normal size were found in CI + IGF animals.
marked changes in cell shape and cytoskeletal organization in different cell lines including cardiomyocytes, mesangial cells, adrenal cells, and human epidermoid carcinoma cells. Microvilli consist of fingerlike projections of the cell membrane with a central core formed by a bundle of actin filaments. Thus, it seems possible that the effect of IGF-I on microvillus shape and absorptive function is mediated in part by changes in cytoskeletal organization. In fact, the density of actin microfilaments at the base of the microvilli, at the site of connection with the intermediate filaments network, was more prominent in both CI + IGF and controls than in CI rats (arrows in Figure 5).

In addition to IGF-I, other hormones, such as glucagon, have been shown to stimulate sugar transport at the enterocyte brush border. This effect of glucagon seems to be mediated by adenosine 3',5'-cyclic monophosphate. Future studies are necessary to elucidate the mechanisms through which IGF-I improves sugar absorption in cirrhosis.

References


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