Inhibitory Effect of Somatostatin Analogue RC-160 on the Growth of Hepatic Metastases of Colon Cancer in Rats: A Study with Magnetic Resonance Imaging

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ABSTRACT

The effect of somatostatin analogue RC-160 on the growth of hepatic metastases of colon cancer was investigated in rats using magnetic resonance imaging. Experimental liver metastatic tumors were established in syngeneic BDIX rats after intrasplenic injection of DHD/K12 colon adenocarcinoma cells. Each rat with implanted liver tumors received s.c. injections of somatostatin analogue RC-160 (50 μg/kg) or the vehicle (control) twice a day for 4 weeks, starting 3 weeks after tumor inoculation. During the treatment with RC-160, the growth of liver tumors was studied quantitatively by measuring liver tumor volumes in vivo with magnetic resonance imaging at intervals of 7 days. Chronic administration of RC-160 inhibited the growth of hepatic metastases of colon cancer in rats. Significant inhibition of liver tumor growth in RC-160-treated rats was observed throughout the treatment. The final liver tumor volume in the treated rats was decreased by 56.1% as compared to the controls. The treatment with RC-160 reduced the percentage increase in liver tumor volume from 1575 ± 674% (mean ± SEM) for the control to 1034 ± 727% in the treated group. The tumor volume doubling time in treated rats was 3.7 days longer than the controls. The liver tumor growth delay time was 15.1 days. At the end of the treatment, the incidence of ascites and the weights of tumorous livers were also decreased by RC-160 treatment. Administration of RC-160 prolonged the median survival time by 13 days in treated rats. In cell cultures, significant inhibitory effects of somatostatin-14 and RC-160 on the growth of DHD/K12 colon cancer cells were determined by MTT assay and [3H]thymidine incorporation assay, indicating direct effects of these peptides on the growth of colon cancer cells in vitro. These data suggest that administration of RC-160 could inhibit the growth of colon cancer and their hepatic metastases in rats. Somatostatin analogue RC-160 might be considered as a potential new agent for the treatment of patients with hepatic metastases of colorectal cancers.

INTRODUCTION

Hepatic metastasis is one of the most frequent and serious complications in patients with colorectal cancers (1). Although considerable efforts have been made by oncologists during past decades, treatment of hepatic metastases of colorectal cancer is still a great challenge, because of the poor therapeutic response of these patients and little, if any, prolongation of survival. Previous studies have revealed that the tumor growth and cellular proliferation of colorectal cancers are under the control of gastrointestinal hormones and growth factors like EGF and IGF-I (2–7). Consequently, it is possible that colorectal tumors could be treated by hormonal manipulation based on different hormonal analogues (5–11). Somatostatin is a regulatory peptide with inhibitory actions on many cells (7, 12). Somatostatin and its analogues have been demonstrated to have powerful antiproliferative effects on various experimental and human malignant tumors (7). In a recent study, we have shown that RC-160, a long-acting/superactive analogue of somatostatin-14, significantly inhibited the growth of implanted tumors of rat colon cancer cells (11). The inhibitory effect of RC-160 on the growth of a human colon cancer in nude mice was also demonstrated (9). These findings suggest a potential application of somatostatin analogue RC-160 in the treatment of hepatic metastases of colorectal cancers.

Quantitative evaluation of the growth of hepatic metastatic tumors in vivo with noninvasive methods has important implications in the study of new therapies in experimental oncology. MRI is a new and powerful diagnostic tool, which provides superior liver images due to its excellent spatial resolution and contrast, especially in soft tissues (13, 14). In experimental oncology, MR imaging has been introduced in a study of the growth of transplanted s.c. prostate tumors in rats (15). Recently, MR imaging has been successfully used for measurement of the volumes of normal livers and experimental liver metastatic tumors of colon cancer in rats (16–18). Using this technique, the growth curve of liver tumors can be quantitatively studied at selected time intervals in the same animals with an acceptable measurement of accuracy (17).

In this study, we treated experimental hepatic metastases of colon cancer in rats by chronic administration of somatostatin analogue RC-160. The effect of RC-160 on the growth of liver tumors was studied in vivo by successive determinations of tumor volumes with MR imaging. Direct effects of somatostatin-14 and RC-160 on the growth of DHD/K12 colon cancer cells were investigated by MTT assay and [3H]thymidine incorporation assay in cell cultures.

MATERIALS AND METHODS

Induction of Liver Metastases. Adult male syngeneic BDIX rats weighing 300–350 g (Animal Unit, V.U.B., Belgium) and DHD/K12 colon cancer cell line, originally established from a 1,2-dimethylhydrazine-induced colon adenocarcinoma in BDIX rats (19), were used in this study. Liver metastatic tumors were induced in rats by intrasplenic injection of DHD/K12 colon cancer cells according to a method reported previously (20). Briefly, after the animals were anesthetized with an i.p. injection of chloral hydrate (10 mg/kg), the spleen of each rat was exposed and 0.5 ml of tumor cell suspension (1 × 106 cells) was injected slowly into the spleen. After 5 min, a splenectomy was carried out and the abdominal wall was closed by sutures. After tumor cell injection, all the animals were given cyclosporin A (Sandoz, Basel, Switzerland) in olive oil (10 mg/kg/day) by a daily esophageal intubation for 3 weeks to facilitate the liver tumor growth (21).

Treatment of RC-160. Somatostatin analogue RC-160 (p-Phe-Cys-Tyr-p-Trp-Lys-Val-Cys-Trp-NH2), originally synthesized as described

Received 4/28/92; accepted 8/26/92.

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1 This work was supported by grants for cancer research from Algemene Spaar en Lijfrente Kas (A. S. L. K.) and F.G.W.O., Belgium.

2 To whom requests for reprints should be addressed, at Department of Surgery, Academic Hospital, Free University of Brussels (A.Z.-V.U.B.), Laarbeeklaan 101, B-1090 Brussels, Belgium.

3 The abbreviations used are: EGF, epidermal growth factor; IGF-I, insulin-like growth factor-I; MRI, magnetic resonance imaging; MR, magnetic resonance; SS-14, somatostatin-14; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide.

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(22), was generously provided by Debiopharm, Lausanne, Switzerland. RC-160 powder was dissolved in 0.1 M acetic acid (5 mg/ml). RC-160 injection solution (50 µg/ml) was prepared freshly in 0.9% NaCl with 0.2% bovine serum albumin (Sigma, St. Louis, MO). All the rats with implanted liver tumors were randomly divided into 4 groups as follows: Group 1, rats with liver tumors treated with RC-160 for MR imaging (x8 rats); Group 2, rats with liver tumors treated as control for MR imaging (x8 rats); Group 3, rats with liver tumors treated with RC-160 for evaluation of survival time (x6 rats); Group 4, rats with liver tumors treated as control for survival study (x6 rats).

Each animal in the treatment groups was given s.c. injections of RC-160 (50 µg/kg) twice per day for 4 weeks. The rats with liver tumors started to receive RC-160 treatment 3 weeks after intrasplenic tumor cell injection.

Measurement of Liver Tumor Volume by MR Imaging. The rats bearing liver tumors in Groups 1 and 2 were submitted to MR imaging weekly for 4 weeks from day 7 of RC-160 treatment. MR imaging was performed under anesthesia with an i.p. injection of sodium pentobarbital (15 mg/kg), and carried out on a SIS 200/330 MR Imaging and Spectroscopy System (SIS, Fremont, CA) at 4.7 T field strength, using a method of MR liver tumor volumetry established previously (17). Contiguous MR liver images with a slice thickness of 3.03 mm were acquired transversely starting from the diaphragm to the lowest margin of each liver without the intersectional space. Approximately 13 MR image slices were obtained for each rat liver. Spin echo pulse sequences (repetition time 2500 ms/echo time 25 ms), averaging 4 acquisitions per image of rat liver, and a retarded phase encoding were used.

The tumor volume in each rat liver was estimated from the MR liver images by summing up the products of cross-sectional areas of liver tumors and the slice thickness (23, 24). In individual MR images, outline of the liver tumor was traced on the computer screen (Sun 3/160 Workstation) with a mouse. The enclosed cross-sectional area of liver tumors was calculated with the VNMR image analysis software package (SISCO, Fremont, CA). The areas of liver tumors in individual slices were summed up to produce the total area of liver tumors and then multiplied by the slice thickness of 3.03 mm to obtain the total liver tumor volume.

Evaluation of Liver Tumor Growth and Survival Time. For estimating the growth rate of liver tumors, the liver tumor volumes were repeatedly measured during the treatment of RC-160 by MR imaging in the same rats at an interval time of 7 days. The values of liver tumor volumes measured by MR imaging were plotted against the time of RC-160 treatment to construct the growth curves of liver tumors. Tumor growth parameters, i.e., tumor growth rate, tumor volume doubling time, tumor growth delay time, etc., were estimated from these growth curves (25). At the end of RC-160 treatment, the rats in Groups 1 and 2 were killed by ether. The livers were resected, weighed, and fixed in 10% neutral formalin for macroscopic examination.

The rats in Groups 3 and 4 were kept until they died, for estimating survival time.

Cell Culture in Vitro. The effects of natural SS-14 (UCB, Brussels, Belgium) and somatostatin analog RC-160 on the growth of DHD/K12 cells in vitro were investigated by both tetrazolium-based colorimetric (MTT) assay and [3H]thymidine incorporation assay. MTT assay was performed according to a method of Mosmann (26). Single cell suspension (2.5 × 10^6 cells/ml) was prepared in RPMI 1640 supplemented with 10% fetal bovine serum. Under continuous stirring, 200 µl of cell suspension were added into each well (5 × 10^5 cells/well) of 96-well flat-bottomed plates. In a preliminary study, this cell seeding density was found to produce 50–70% confluence after DHD/K12 cells were cultured in the serum-free medium supplemented with 0.3% bovine serum albumin, insulin (10 µg/ml), transferrin (10 µg/ml), and 1% sodium pyruvate (100 mM) for 6–7 days. After the cells were cultured for 24 h, the culture medium in each well was replaced by 200 µl of fresh supplemented serum-free medium containing different concentrations of SS-14 or RC-160. The same volume of the serum-free medium but without the tested drugs, was added to the control wells. The medium was changed once after 3 days of culture. After an additional 3 days of culture, 20 µl of MTT solution (5 mg/ml; Sigma) was added to each well and incubated at 37°C for 6 h. The spent medium (100 µl) was removed from each well, leaving 120 µl medium/well, and then 100 µl of 1% sodium dodecyl sulfate-0.01 N HCl solution were added into the well. The plates were incubated overnight to dissolve the formed formazan crystals in the cells. The absorbance of the released formazan product in each well was measured spectrophotometrically by an Emax microplate reader (Molecular Devices Co., Menlo, CA) at a wavelength of 540 nm.

All tests were performed in quadruplicate and repeated twice.

For [3H]thymidine incorporation assay (27), 1 ml of cell suspension (5 × 10^6 cells) in RPMI 1640 with 10% fetal bovine serum was added to each well of (24-well) culture dishes. After 24 h, the medium was replaced by serum-free medium without supplements, except for antibiotics. After another 24 h of incubation, the medium was replaced by 1 ml of the serum-free medium containing different doses of RC-160 or SS-14. The same volume of serum-free medium but without RC-160 or SS-14 was used for controls. The cells were cultured without or without RC-160 or SS-14 for 5 h and then were pulsed with [methyl-3H]-thymidine (radioactivity, 25 Ci/mmol; Amersham, Buckinghamshire, United Kingdom) at a dose of 1 µCi/well for 1 h. At the end of the incubation, the medium in each well was replaced with 1 ml Camoy’s solution (methanol:glacial acetic acid, 3:1 v:v) to fix the cells overnight. The wells were then washed twice with fresh Camoy’s solution and once with methanol and allowed to dry completely. Trypsin (1.5 mg/ml phosphate-buffered saline) was added to each well and the plates were incubated for 4 h at 37°C to dissolve the cells. The trypsin solution was collected and replaced with 0.5 ml of 1% sodium dodecyl sulfate solution. Following a 1-h incubation, this solution was collected and pooled with trypsin solution. An aliquot (0.5 ml) of the cell digest was mixed with 2 ml of scintillation mixture and counted for 1 min by a liquid scintillation counter.

RESULTS

Volumes of Liver Tumors after RC-160 Treatment as Measured by MRI. Experimental hepatic metastases were established in 28 BDIX rats after intrasplenic injection of DHD/K12 colon cancer cells. In Groups 1 and 2, 4 rats with ascites died from the effects of anesthesia at the time of MR imaging, and were excluded from further study. Successive measurements of liver tumor volumes with MR imaging were completed in the remaining 6 rats in each group throughout the experiment.

Excellent MR liver images, with high resolution in soft tissues and adequate contrast between liver tumors and liver parenchyma, were obtained (Fig. 1, A and B). Liver tumors, as well as intra- and extrahepatic anatomic structures, were clearly visualized in the cross-sections of MR images at the upper abdomen of rats. Changes in the growth of liver metastases in individual animals were quantitatively monitored for 4 weeks by sequential measurements of the volumes of liver tumors at intervals of 7 days. The growth curves of hepatic metastatic tumors, which were constructed from the tumor volumes measured by MR volumetry during the RC-160 treatment, are shown in Fig. 2. Chronic administration with somatostatin analogue RC-160 inhibited the growth of hepatic metastases of DHD/K12 cells in rats (Table 1) (Fig. 2). The suppressive effect of RC-160 on the growth of liver tumors was observed in terms of MR liver tumor volume throughout the RC-160 treatment. A significant inhibition of liver tumor growth in the rats of the treatment group, as compared with the controls, occurred from Week 2 to Week 4 of the treatment (P < 0.01). At the end of the treatment, the final liver tumor volume in the RC-160 group was reduced by 56.1%, compared to the control. Similar inhibition was seen when the percent increase in tumor volume was examined. Comparing the liver tumor volumes between Week 1 and Week 4, the control tumors increased 1575 ± 674% (SEM),

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but the treatment with RC-160 resulted in a percentage increment of liver tumor volumes of only 1034 ± 727% (P < 0.01). The tumor volume doubling time in the treatment group was prolonged 3.7 days by the RC-160 treatment. In the treatment group, the time required for the tumors in each liver to grow to a volume of 6000 mm$^3$ was delayed to 15.1 days (tumor growth delay time) longer than that in the control.

Pathological Findings after RC-160 Treatment. The inhibitory effect of RC-160 on the growth of hepatic metastases of colon cancer was also demonstrated by the pathological findings at termination of the treatment (Table 2). Although there was no difference in the number of rats developing hepatic metastases between the RC-160 treatment group and the control group, the number of rats with ascites (2 of 6) in the RC-160 treatment group was much lower than that (5 of 6) of the control (P < 0.01). After the RC-160 treatment, the mean weight of livers with metastatic tumors in the treatment group was only 54.4% of that in the control (P < 0.01).

Survival Time after RC-160 Treatment. The life-span of rats with hepatic metastatic tumors (Groups 3 and 4) was significantly prolonged by administration of RC-160 (Fig. 3). After 4 weeks of RC-160 treatment, the median survival times of rats in the control and the RC-160 treatment groups were 48 and 61 days, respectively (P < 0.01). Treatment with RC-160 increased the median survival time in the RC-160-treated rats by 13 days.

Effects of RC-160 and Somatostatin-14 on Cell Growth in Vitro. After 6 days of culture in serum-free medium, inhibitory effects of RC-160 and SS-14 were observed by MTT assay on the growth of DHD/K12 cells in vitro (Fig. 4). Addition of RC-160, from concentrations of $10^{-8}$ to $10^{-6}$ M to the cell culture, resulted in a 19–21% decrease in the growth of the treated cells, compared to the control (P < 0.01). Maximal inhibition of cell growth was found at $10^{-7}$ M concentration of RC-160. An increase of the dose of RC-160 to $10^{-6}$ M did not produce a further inhibition of cell growth. A similar inhibitory effect was observed after the cells were exposed to SS-14 (Fig. 4). The addition of SS-14 at doses between $10^{-8}$ and $10^{-6}$ M to the cell culture also induced a small (6–11%) but significant inhibition in the cell growth in vitro (P < 0.01).

Effects of RC-160 and Somatostatin-14 on Cell Proliferation in Vitro. In $[3H]$thymidine incorporation assay, the DNA synthesis by DHD/K12 cells was significantly inhibited by either

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**Table 1** Effect of somatostatin analogue RC-160 on the volumes and growth of liver metastatic tumors of colon cancer in rats as measured by MRI

<table>
<thead>
<tr>
<th>Group</th>
<th>Liver tumor volume (mm$^3$) by MRI</th>
<th>(% Increase of tumor vol.$^a$)</th>
<th>Tumor growth rate (mm$^3$/day)</th>
<th>Tumor vol. doubling time (days)</th>
<th>Tumor growth delay time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>2,358 ± 871$^c$ (37,4,213)$^d$</td>
<td>14,064 ± 1,828 (9,749–19,502)$^d$</td>
<td>1,575 ± 674</td>
<td>526.6</td>
<td>9.5</td>
</tr>
<tr>
<td>RC-160</td>
<td>1,675 ± 441 (11–3,226)$^d$</td>
<td>6,138 ± 604$^c$ (611–7,555)$^d$</td>
<td>1,034 ± 727$^e$</td>
<td>226.4</td>
<td>13.2</td>
</tr>
</tbody>
</table>

$^a$ The MR liver tumor volume on Day 28 of RC-160 treatment was compared with that on Day 7.

$^b$ The day after the treatment of RC-160.

$^c$ Mean ± SEM.

$^d$ Range of the values.

$^e$ RC-160 versus control, P < 0.01.
Table 2 Effect of somatostatin analogue RC-160 on the growth of liver metastases of colon cancer in rats

<table>
<thead>
<tr>
<th>Group</th>
<th>Body wt (g)</th>
<th>No. of rats with liver tumors</th>
<th>Tumorous liver weight (g)</th>
<th>% inhibition</th>
<th>No. of rats with ascites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>374.5 ± 10.3a</td>
<td>6/6</td>
<td>32.08 ± 5.76c</td>
<td></td>
<td>5/6</td>
</tr>
<tr>
<td>RC-160</td>
<td>343.2 ± 4.1b</td>
<td>6/6</td>
<td>17.45 ± 1.47c</td>
<td>45.6</td>
<td>2/6c</td>
</tr>
</tbody>
</table>

*a Mean ± SEM.  
*b Versus control, P < 0.05.  
*c Versus control, P < 0.01.

Fig. 3. Survival time of rats with liver metastases of colon cancer after treatment with RC-160. The median survival time of rats in the RC-160 treatment group was 13 days longer than that in the control.

RC-160 or SS-14, after a short-term culture. The uptake of [3H]thymidine by the tumor cells decreased in a dose-dependent manner when increasing doses of RC-160 were added in the culture medium (Fig. 5A). After the tumor cells were exposed to RC-160 at a concentration of 10^{-6} M, the [3H]thymidine incorporation was inhibited by 34.1%, as compared to the control (P < 0.01). The reduction in the uptake of [3H]thymidine was also observed after the tumor cells were cultured with SS-14, but the inhibition was not as pronounced as in the case of RC-160 (Fig. 5B). The [3H]thymidine incorporation was inhibited by 23.4% at 10^{-6} M concentration of SS-14 as compared to the control (P < 0.01).

DISCUSSION

Methods to measure the volume of implanted liver tumors in rats using MR imaging have been established recently (17, 18). In the present study using MR imaging, we visualized and quantitatively studied, for the first time, the growth of experimental liver metastases of DHD/K12 colon cancer cells in rats treated with somatostatin analogue RC-160. In the evaluation of new therapies against hepatic metastases, especially when the change of liver tumor growth needs to be continuously studied, measurement of the volumes of liver tumors with the noninvasive method of MR imaging may provide more valuable and quantitative information about the growth of liver tumors in vivo, than the previously used in vitro method, based on counting the tumors on the liver surface and measuring their size after killing the animals.

With MR volumetry, we were able to demonstrate the inhibitory effect of RC-160 on the growth of hepatic metastases of DHD/K12 colon cancer cells in BDIX rats throughout the treatment. Chronic administration of RC-160 resulted in a significant suppression of liver tumor growth, as evidenced by the reduced tumor volumes. Growth inhibition obtained at the end of the treatment was 50–60%. Treatment with RC-160 lowered tumor growth rate and prolonged tumor volume doubling time. The changes in liver tumor volumes obtained by MR volumetry were supported by pathological evidence showing that the tumorous liver weight and the incidence of ascites were also reduced by RC-160 treatment. The rats receiving the RC-160 treatment survived significantly longer than the controls. Our findings suggest that somatostatin analogue RC-160 could be considered for the treatment of patients with hepatic metastases of colorectal cancers.

The observations obtained in the present study extend our earlier results about the inhibitory effect of RC-160 on the
growth of implanted s.c. tumors of colon cancer in rats (11). In
the earlier study, the inhibitory effect of RC-160 on the tumor
growth was observed after the administration of RC-160 start-
ing on the day of tumor implantation, when the initial tumor
volume was very small. In the present study, a significant in-
boration of RC-160 on the growth of liver tumors was recorded in
rats receiving the injections of RC-160 even at 3 weeks after
intraperitoneal injection of tumor cells, when the liver tumors had
already grown to a large size. Therefore, it appears that treat-
ment with RC-160 suppresses the tumor growth of colon cancer
not only in the initial stages, but also in the phase of logarithmic
growth. This implies that RC-160 could be possibly applied for
the treatment of patients with advanced colorectal cancer or
liver metastases.

The mechanism of the inhibitory effect of RC-160 on the
growth of hepatic metastases of colon cancer cells is still not
clear. Previous studies have indicated that both direct and in-
direct mechanisms could be involved in the inhibition of the
cancer cell growth (7). Smith and Solomon (5) have shown that
somatostatin could directly inhibit the growth of HT-29 human
colon cancer cells in vitro. Although we demonstrated previ-
ously that somatostatin analogue RC-160 inhibited the growth of
s.c. tumors of DHD/12 rat colon cancer cells in vivo, we were
unable to show direct effects of somatostatin-14 or RC-160 on
the growth of DHD/K12 cells in 5-day cultures in serum-free
medium (11). It is possible that inhibitory effects of somato-
statin and its analogue were masked by the slow growth of tumor
cells in this culture medium. In fact, it was found that the
growth of DHD/K12 cells in serum-free medium was slowed
down, or even stopped after 3 days of culture, presumably due
to the lack of nutrients and growth promoting factors that are
necessary to maintain the proliferation of tumor cells in vitro.
Therefore, in the present study, we improved the culture con-
ditions by adding 0.3% bovine serum albumin and several
growth-stimulating peptides to the serum-free medium, so that
the cells could not only survive, but also proliferate after 6–7
days of culture in vitro. Using this supplemented serum-free
medium and a more sensitive MTT assay, we were able to show
that the growth of DHD/K12 cells in vitro was significantly
inhibited, both by natural somatostatin-14 and synthetic ana-
logue RC-160. The inhibitory effects of somatostatin and ana-
logue RC-160 on tumor cell growth were confirmed by obser-
ations with [3H]thymidine incorporation assay. The uptake of
[3H]thymidine by the tumor cells was also significantly inhib-
ited by SS-14 or RC-160 in short-term cultures. Our observa-
tions suggest that SS-14 and RC-160 may exert direct actions
on the growth of DHD/K12 cells in vitro, which are mediated
by somatostatin receptors. Recently, specific receptors for soma-
tostatin and RC-160 were found on the membranes of human
colon cancers and HT-29 human colon cancer line (28). 
Whether the receptors for somatostatin or RC-160 also exist on
the membrane of DHD/K12 rat colon cancer cells will be sub-
ject of future investigations.

Another possible explanation for the inhibitory effects of
RC-160 on the growth of colon cancer cells in vivo is the sup-
pression of the release or action of gastrin or the interference
with the secretion, action, or receptors of growth factors. It is
known that the growth of colon cancer may be influenced by
gastrointestinal hormones and growth factors like EGF and
IGF-I (2, 4, 7). Somatostatin and its analogues inhibit the ac-
tion, release, and synthesis of gastrin (7, 29). In cell cultures, we
have observed that human gastrin-17 (10−7 M/liter) and EGF
(10 ng/ml) could stimulate the growth of DHD/K112 cells by
59% and 30%, respectively, as based on [3H]thymidine incor-
poration (data not shown). RC-160 and other somatostatin an-
alogues decrease IGF-I levels (7). It has been also found that
RC-160 could inhibit the EGF-induced growth of pancreatic
cancer cells by dephosphorylation of the EGF receptors (30,
31). It is thus possible that the inhibitory effect of RC-160 on
the growth of hepatic tumors of colon cancer in this study might
have been mediated indirectly through the interference with the
release and trophic action of gastrin as well as with the endo-
crine, autocrine, or paracrine effects of growth factors on tumor
growth (7).

Somatostatin and its analogues display multiple physiologi-
and pharmacological functions in several systems, including
the reduction of blood flow in the portal vein and the stimula-
tion of the reticuloendothelial system in the liver (32). The
possible decrease by RC-160 of the portal flow to the liver and
the enhancement of the function of reticuloendothelial compo-
nents in the liver, through which the growth of liver tumors are
suppressed, could also be considered. In addition, the involve-
ment of RC-160 in the inhibition of angiogenesis and the re-
duction of vascularity in tumors is also possible.

In this study, the mean body weights in RC-160-treated rats
were comparatively lower than those in the controls. This dif-
ference is related to the significant reduction in the incidence of
ascites and decreased tumorous liver weights in the rats treated
with RC-160, and not to any toxic effect of RC-160. Previous
studies on implanted s.c. tumors of colon cancers showed that
administration of the same dose of RC-160 to BDIX rats (11)
or higher doses of RC-160 to nude mice (9) did not induce loss of
body weights or any detectable side effects. Phase 1 clinical
trials with RC-160 in patients with advanced exocrine pancre-
catic cancer also demonstrate that RC-160 is well tolerated by
patients even at doses as high as 1500 μg/day (33, 34). Only
minimal side effects, such as diarrhea, have been detected, which
are easily controlled by medication (33, 34).

In conclusion, our data suggest that the measurement of liver
tumor volumes by MRI may provide a new method of evaluat-
ing the response to the treatment of hepatic tumors in vivo. Our
findings also indicate that somatostatin analogue RC-160 may
be potentially useful for the treatment of patients with liver
metastases of colorectal cancers.

ACKNOWLEDGMENTS

The authors thank Dr. F. Miot, Biomedical Nuclear Magnetic Reson-
ance Unit, U.L.B., Belgium, for the help in nuclear magnetic reso-
nance imaging.

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