Original Article

Imatinib Mesylate-Incorporated Nanoparticle-Eluting Stent Attenuates In-Stent Neointimal Formation in Porcine Coronary Arteries

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Aim: The use of currently marketed drug-eluting stents (DES) presents safety concerns, including an increased risk for late thrombosis in the range of 0.6% per year in patients, including acute coronary syndrome, which is thought to result from delayed endothelial healing effects. A new DES system targeting vascular smooth muscle cells without adverse effects on endothelial cells is therefore needed. Platelet-derived growth factor (PDGF) plays a central role in the pathogenesis of restenosis; therefore, we hypothesized that imatinib mesylate (PDGF receptor tyrosine kinase inhibitor) encapsulated bioabsorbable polymeric nanoparticle (NP)-eluting stent attenuates in-stent neointima formation.

Methods: Effects of imatinib-incorporated NP-eluting stent on neointima formation and endothelial healing were examined in a pig coronary artery stent model. Effects of imatinib-NP were also examined in cultured cells.

Results: In a cultured cell study, imatinib-NP attenuated the proliferation of vascular smooth muscle cells associated with inhibition of the target molecule (phosphorylation of PDGF receptor-β), but showed no effect on endothelial proliferation. In a pig coronary artery stent model, imatinib-NP-eluting stent markedly attenuated in-stent neointima formation and stenosis by approximately 50% as assessed by angiographic, histopathological, and intravascular ultrasound imaging analyses. Imatinib-NP-eluting stent also attenuated MAP kinase activity, but did not affect inflammation and re-endothelialization.

Conclusion: These data suggest that suppression of neointima formation by a imatinib-NP-eluting stent holds promise as a molecular-targeting NP delivery system for preventing in-stent restenosis.


Key words: Nanotechnology, Drug delivery system, Restenosis, Stents, Smooth muscle cells

Introduction

Although polymer-coated drug-eluting stents (DES) can reduce restenosis and target-vessel revascularization to rates below 10% by its anti-proliferative effects on vascular smooth muscle cells (VSMC), increased risk of late in-stent thrombosis resulting in acute coronary syndrome (unstable angina, acute myocardial infarction and death) after the use of DES devices has become a major safety concern. These adverse effects are thought to result mainly from delayed healing effects of the drugs or polymers on endothelial cells leading to impaired arterial healing processes (impaired endothelial regeneration, excessive inflammation, proliferation and fibrin deposition). Cell-specific molecular targeting against VSMC proliferation without negative effects on endothelial cells,
therefore, is an essential requirement to develop more efficient and safer DES in the future.

Platelet-derived growth factor (PDGF), expressed by VSMC, plays a central role in the pathogenesis of restenosis. Mechanical forces, such as stent-induced overstretch, stimulate VSMC expression and release of PDGF in animals \(^\text{7,8}\) and humans \(^\text{9,10}\). Imatinib mesylate is an inhibitor for c-Abl tyrosine kinase, c-Kit receptor kinase, and PDGF receptor tyrosine kinase \(^\text{11,12}\) and is approved for the treatment of patients with chronic myeloid leukemia. It has been shown that c-Kit-positive progenitor cells can differentiate into \(\alpha\)-actin-positive VSMCs and may contribute to neointima formation \(^\text{13}\). It has also been reported that c-Abl tyrosine kinase is involved in angiotensin II-induced VSMC hypertrophy \(^\text{14}\). Imatinib is reported to be a significantly more potent inhibitor of VSMC proliferation than other inhibitors of PDGF receptor (AGL-2043), with IC\(_{50}\) < 10 nM \(^\text{15}\). In contrast, imatinib has little effect on vascular endothelial cell growth factor receptor tyrosine kinase or endothelial cell proliferation \(^\text{15}\). These data provide a rationale for the use of imatinib mesylate in the prevention of neointima formation associated with in-stent restenosis as a VSMC-specific molecular-targeting drug.

Prior studies have reported that systemic oral administration of imatinib inhibited balloon injury-induced neointima formation in rats \(^\text{11}\) when dosages beyond the clinical norm were used (50 mg/kg per day). In contrast, imatinib had no effect on in-stent neointima formation in rabbits when administered at a clinically relevant dosage (10 mg/kg per day) \(^\text{16}\). Recent clinical studies in humans have detected no beneficial effects of the oral administration of imatinib (600 mg/day for 10 days) \(^\text{17}\) on in-stent restenosis. These data suggest that systemic administration of imatinib at clinical dosages may not be sufficient to antagonize PDGF-induced vascular responses. Furthermore, it was reported the polymer-coated stents with imatinib (600 \(\mu\)g/stent) had no effect on neointima formation in a porcine coronary in-stent stenosis model \(^\text{15}\). This was probably because of unsuitable release characteristics of imatinib from polymer-coated stents. It is suggested that the present polymer coating DES technology is not useful for coating water-soluble drugs such as imatinib. Therefore, preventing in-stent restenosis via imatinib-mediated PDGF-R signaling blockade requires a new efficient drug delivery system. We previously succeeded in developing bioabsorbable polymeric nanoparticles (NP) formulated from the polymer poly (DL-lactide-co-glycolide) (PLGA) \(^\text{18}\), and in formulating a NP-eluting stent by cation electrodeposition coating technology \(^\text{19}\). This NP-eluting stent system provided an effective means of delivering NP-incorporated drugs or genes that target intracellular proteins involved in the pathogenesis of in-stent neointima formation.

Therefore, we hypothesized that imatinib-NP-eluting stent can be an innovative therapeutic strategy for preventing in-stent neointima formation \(\text{in vivo}\). We used a porcine coronary artery in-stent stenosis model and investigated whether imatinib-NP-eluting stent attenuates in-stent neointima formation without adverse effects on arterial healing processes \(\text{in vivo}\).

**Materials and Methods**

**Vascular Smooth Muscle Cell Proliferation Assay**

Human coronary artery VSMCs (Lonza, Walkersville, MD, USA) were cultured and placed into 48-well culture plates (5000 cells per well; BD). Proliferation was stimulated by the addition of PDGF at 10 ng/mL (Sigma, Tokyo, Japan) \(^\text{20}\). Various concentration of imatinib (Novartis Pharma) at 0.1, 1, and 10 \(\mu\)M, imatinib-loaded PLGA NP (PLGA at 0.5 mg/mL containing imatinib at 10 \(\mu\)M), or vehicle alone was added to the wells, and four days later, the cells were fixed with methanol and a single observer counted the number of cells/plate.

**Endothelial Cell Proliferation Assay**

Human umbilical vein endothelial cells (HUVEC) were obtained, cultured, and used between passages 4 to 8 \(^\text{21}\). Recombinant human VEGF165 (10 ng/mL; R&D) or PDGF at 10 ng/mL was added to the basal medium, and cells (7500 cells per well) were incubated in the presence or absence of imatinib, imatinib-NP, or vehicle for 4 days in 48-well culture plates. Cell count assay was performed as stated above.

**Preparation of NP-Eluting Stents by Cationic Electrodeposition Coating Technology**

A lactide/glycolide copolymer (PLGA) with an average molecular weight of 20,000 and a lactide to glycolide copolymer ratio of 75:25 (PLGA7520; Wako Pure Chemical Industries, Osaka, Japan) was used as wall material for the NP. Chitosan was used to coat the surface of PLGA NP. Polyvinylalcohol (PVA-403; Kuraray, Osaka, Japan) was used as a dispersing agent. PLGA NP incorporated with the fluorescent marker fluorescein isothiocyanate (FITC; Dojindo laboratories, Kumamoto, Japan) or with imatinib (purchased from a pharmacy) were prepared by a previously reported emulsion solvent diffusion method in purified water \(^\text{19,22,23}\).

The mean particle size was analyzed by the light
scattering method (Microtrack UPA150; Nikkiso, Tokyo, Japan). A sample of nanoparticulate suspension in distilled water was used for particle size analysis. The average diameter of FITC- and imatinib-incorporated NP was about 200 nm. Size distribution was similar between FITC-NP and imatinib-NP (see Fig. 1). FITC- and imatinib-encapsulated PLGA NP contained 5.0% (w/w) FITC and 8.3% (w/w) imatinib, respectively. The zeta potential of the NP as measured by Zetasizer Nano Z (Malverm, America) was +6.7 and +10.0 mV, respectively.

The 16 mm-long stainless-steel, balloon-expandable stents (Multilink) were ultrasonically cleaned in acetone, ethanol, and demineralized water. The cathodic electrodeposition coating was prepared on cathodic stents in NP solution at a concentration of 5 g/L in distilled water with a current maintained between 2.0 and 10.0 mA by a direct current power supply (DC power supply; Nippon Stabilizer Co, Tokyo, Japan) for different periods under sterile conditions. The coated stents were then rinsed with demineralized water and dried under a vacuum overnight. This electrodeposition coating procedure produced a coating of approximately 250 ± 40 μg of the polymer NP per stent and 21 ± 8 μg of imatinib per stent (n = 12). The surface of some NP-coating stents were observed with scanning electron microscopy (JXM8600; JEOL, Tokyo, Japan).

Prior to experimental use, non-coated bare metal and NP-coated stents were mounted mechanically over the 3-mm balloon for implantation in the coronary artery. These balloon-mounted stent sets were sterilized using ethylene oxide.

Animal Preparation and Stent Implantation
All in vivo experiments were reviewed and approved by the Committee on Ethics in Animal Experiments, Kyushu University Faculty of Medicine, according to the Guidelines of the American Physiological Society. This study also conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

Domestic male pigs (Kyudo, Tosu, Japan; aged 2 to 3 months and weighing 25 to 30 kg) received oral aspirin (330 mg/day) and ticlopidine (200 mg/day) until euthanasia from 3 days before the stent implantation procedure. Animals were anesthetized with ketamine hydrochloride (15 mg/kg, IM) and pentobarbital (20 mg/kg, IV). They were then intubated and mechanically ventilated with room air. A preshaped Judkins catheter was inserted into the carotid artery and advanced to the orifice of the left coronary artery. After systemic heparinization (100 IU/kg) and intracoronary administration of nitroglycerin, coronary angiography of the left coronary artery was performed using contrast media (iopamidol 370®) in a left oblique view with an angiography system (Toshiba Medical, Tokyo, Japan). Animals were divided into 3 groups, which underwent deployment of either a non-coated bare metal stent (2 week; n = 4 for Western blot analysis, 4 week; n = 10 for angiographic, histopathological and intravascular ultrasound analyses), FITC- incorporated NP-eluting stents (4 week; n = 10 for angiographic, histopathological and intravascular ultrasound analyses), or imatinib-incorporated NP-eluting stents (2 week; n = 4 for Western blot analysis, 4 week; n = 10 for angiographic, histopathological and intravascular ultrasound analyses), to either the left anterior descending (LAD) or the left circumflex coronary (LCx) arteries.

A segment with a mean coronary diameter of 2.5 mm was selected by using quantitative coronary angiography (Toshiba Medical, Tokyo, Japan) with a stent-to-artery ratio of approximately 1.1 to 1.2 (Table 1). A balloon catheter mounted with a stent was then advanced to the pre-selected coronary segments for deployment over a standard guidewire. The balloon catheter was inflated at 12 atm for 60 seconds once and thereafter deflated, and was then slowly withdrawn, leaving the stent in place.

Quantitative coronary angiography (Toshiba Medical, Tokyo, Japan) was performed before, immediately after, and 4 weeks after stent implantation to examine the coronary arterial diameter at stented and non-stented sites. An image of a Judkins catheter was used as the reference diameter. Arterial pressure, heart...
rate, and ECG were continuously monitored and recorded on a recorder.

Intravascular Ultrasound
Intravascular ultrasound imaging (IVUS) was performed to assess the extent of neointima formation in vivo 4 weeks after stent implantation. Imaging was performed using a 40 MHz ultrasonic imaging catheter (Ultra cross; Boston Scientific, Boston, USA) and an automatic pullback device, and the studies were recorded on 1/2-inch high-resolution s-VHS tapes for off-line volumetric assessment. Because of the limited availability of IVUS probes, IVUS was performed 7 and 8 pigs in FITC-NP and imatinib-NP stent groups, respectively.

Histopathological Study
Four weeks after the coronary angiographic study, animals were euthanized with a lethal dose of sodium pentobarbital (40 mg/kg intravenously), and histological analysis was performed. The left coronary artery was perfused with 10% buffered formalin at 120 mm Hg and fixed for 24 hours. The stented artery segments were isolated and processed as described previously. The segment was cut at the center of the stent and embedded in methyl methacrylate mixed with n-butyl methacrylate to allow for sectioning through the metal stent struts. Serial sections were stained with elastica van Gieson and with hematoxylin-eosin (HE). The neointimal area, the area within the internal elastic lamina (IEL), and the lumen area were measured by computerized morphometry, which was carried out by a single observer who was blinded to the experimental protocol. All images were captured by an Olympus microscope equipped with a digital camera (HC-2500) and were analyzed using Adobe Photoshop 6.0 and Scion Image 1.62 Software. The injury, inflammation, and re-endothelialization scores were determined at each strut site, and mean values were calculated for each stented segment.

Western Blot Analysis
For in vitro study, protein was extracted from cultured VSMC, and protein expression was analyzed using antibodies against human PDGF receptor-β (0.1 mg/mL; R&D Systems Inc.), phospho-PDGF receptor-β (0.5 mg/mL; R&D), or anti-actin (Sigma).

For in vivo study, animals were euthanized with a lethal dose of sodium pentobarbital (40 mg/kg intravenously) two weeks after stent implantation when the neointima was modestly formed, and Western blot analysis was performed. Protein was extracted from frozen arterial tissues excised from stented coronary arterial segments (LAD or LCx) and non-stented normal coronary arterial segments (right coronary artery). Cell extracts (20 μg) were resolved on 10% reducing SDS-PAGE gels and blotted onto nitrocellulose membranes (Bio-Rad, Hercules, CA). Protein expression was analyzed using antibodies against MAP kinase (ERK1/2) (0.5 mg/mL; R&D Systems Inc.), phospho-ERK1/2 (1:2000; Cell Signaling), or anti-actin (Sigma). Immune complexes were visualized with horseradish peroxidase-conjugated secondary antibodies (Pierce, Rockford, IL) using the ECL Plus system (Amersham Biosciences). Western blot analysis was performed with sequential antibodies and was detected with the ECL Detection Kit (Amersham).

Statistical Analysis
Data are expressed as the means ± SE. Statistical analysis of differences between two groups was performed with the unpaired t-test, and the statistical analysis of differences among three or more groups was assessed using ANOVA and multiple comparison tests. P values < 0.05 were considered significant.

Results
In vitro Effects of Imatinib on Proliferation of Vascular Smooth Muscle Cells and Endothelial Cells
We previously reported (1) the in vitro time course of FITC release from FITC-incorporated NP, and (2) highly efficient and stable delivery of NP into the cytoplasm of SMC and endothelial cells. In the present study, we examined in vitro effects of imatinib and imatinib-NP. As reported by others, imatinib attenuated the PDGF-induced proliferation of human coronary arterial SMC in a dose-dependent manner (Fig. 2A). Imatinib-NP also prevented the PDGF-induced responses of SMC. Western blot analysis showed that in human coronary artery SMC, both imatinib and imatinib-NP inhibited PDGF-induced phosphorylation of PDGF receptor-β in a dose-dependent manner (Fig. 2B). In contrast, neither imatinib nor imatinib-NP affected VEGF- and PDGF-induced proliferation of human endothelial cells (Fig. 2C).

Effects of Imatinib-NP-Eluting Stent on Neointima Formation 4 Weeks After Stent Implantation
Three animals (2 in control bare metal stent group and 1 in FITC-NP-eluting stent group) died suddenly between weeks 3 and 4; therefore, these animals were excluded from angiographic and histopathological analyses. These analyses were performed in 27
pigs (8 in control bare metal stent group, 9 in FITC-NP-eluting stent group, and 10 in imatinib-NP eluting stent group).

Quantitative coronary arteriography revealed that (1) there was no significant difference in the coronary diameter before and immediately after stent implantation and the stent-to-artery ratio among the 3 groups; and (2) the coronary diameter was less in
the control bare metal and FITC-NP-eluting stent sites than in the imatinib-NP-eluting stent sites 4 weeks after stenting (Table 1). Thus, angiographically, in-stent stenosis was less in the imatinib-NP group than in the control and FITC-NP group (Fig. 3A and B).

Intravascular ultrasound imaging (IVUS) could be performed in FITC-NP (n=7) and imatinib-NP stent (n=8) groups, which demonstrated that the extent of neointima formation was significantly less at the imatinib-NP stent site than at the FITC-NP-stent site (Fig. 3C).

Histological analysis demonstrated that a signifi-
cant in-stent neointima formed similarly at the non-coated bare metal stent and FITC-NP-eluting stent sites. Quantitative analysis demonstrated a significant reduction in neointima formation at the imatinib-NP-eluting stent site (Fig. 4). In contrast, there were no significant differences in IEL and EEL areas among all 3 groups (Table 2). A semiquantitative histological scoring system demonstrated no significant difference in the injury score and inflammation score among the 3 groups (Table 3). Endothelial cell linings were
Table 2. Histopathological analysis of in-stent neointima formation 4 weeks after stent implantation in porcine coronary artery

<table>
<thead>
<tr>
<th></th>
<th>Bare metal control stent (n = 8)</th>
<th>FITC-NP-eluting stent (n = 9)</th>
<th>imatinib-NP-eluting stent (n = 10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area within the IEL, mm²</td>
<td>4.56 ± 0.11</td>
<td>4.54 ± 0.09</td>
<td>4.84 ± 0.14</td>
<td>0.13</td>
</tr>
<tr>
<td>Area within the EEL, mm²</td>
<td>5.72 ± 0.18</td>
<td>5.76 ± 0.10</td>
<td>5.96 ± 0.14</td>
<td>0.40</td>
</tr>
<tr>
<td>Lumen area, mm²</td>
<td>2.18 ± 0.38</td>
<td>2.11 ± 0.24</td>
<td>3.41 ± 0.23**</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are the mean ± SEM. *p < 0.05, **p < 0.01 versus control bare metal stent.

Table 3. Re-endothelialization, injury score, and inflammation score 4 weeks after stenting

<table>
<thead>
<tr>
<th></th>
<th>Bare metal control stent (n = 8)</th>
<th>FITC-NP-eluting stent (n = 9)</th>
<th>imatinib-NP-eluting stent (n = 10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re-endothelialization score</td>
<td>3 ± 0</td>
<td>3 ± 0</td>
<td>3 ± 0</td>
<td>1.0</td>
</tr>
<tr>
<td>Injury score</td>
<td>1.75 ± 0.09</td>
<td>1.79 ± 0.09</td>
<td>1.88 ± 0.08</td>
<td>0.57</td>
</tr>
<tr>
<td>Inflammation score</td>
<td>1.70 ± 0.14</td>
<td>1.62 ± 0.08</td>
<td>1.75 ± 0.06</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Data are the mean ± SEM. The re-endothelialization score was defined as the extent of the circumference of the arterial lumen covered by endothelial cells and was scored from 1 to 3 (1 = 25%; 2 = 25% to 75%; 3 ≥ 75%).

Effects of Imatinib-NP-Eluting Stent on Protein Expression of MAP Kinase in vivo

Western blot analysis was performed in another set of animals, which underwent deployment of both a bare metal stent and imatinib-NP-eluting stent to either LAD or LCx. On day 14 post-stenting, the neointima, and the media and adventitia were harvested. Protein expression of the phosphorylation of ERK was significantly less at the imatinib-NP-eluting stent site than at the bare metal stent site (Fig. 5). In contrast, no significant changes were found in phosphorylated ERK expression in the media and adventitia.

Discussion

We here report the first successful development of imatinib-NP-eluting stents with a newly invented cation electrodeposition coating technology. Importantly, this NP-mediated drug delivery platform is able to carry hydrophilic agents such as imatinib, which offers advantages over the current stent-coating technology. We here showed that (1) imatinib-NP caused the cell-specific targeting of VSMC proliferation associated with inhibition of the target molecules of imatinib (phosphorylation of PDGF receptor-β) in vitro; (2) imatinib-NP showed no negative effects on the proliferation of endothelial cells in vitro, and (3) imatinib-NP-eluting stent effectively attenuated in-stent stenosis (neointima formation) by about 50% as compared to bare metal stents and FITC-NP eluting stents in porcine coronary arteries without apparent negative effects on the endothelial healing process in vivo.
extracellular space as PLGA is hydrolyzed, resulting in prolonged delivery of imatinib into the stented coronary artery. In this regard, we recently reported that this bioabsorbable polymeric NP-eluting stent system has unique aspects in vascular compatibility and an efficient drug delivery system (stable delivery of NP into the neointima and medial layers until day 28 after deployment of a NP-eluting stent), compared to a dip-coated polymer-eluting stent.

In contrast to our present findings, prior studies failed to demonstrate the inhibitory effect of imatinib on in-stent neointima formation in rabbits (oral administration at 10 mg/kg per day for 6 weeks)\textsuperscript{19}, pigs (600 μg/stent)\textsuperscript{19}, and patients (oral administration at 600 mg/body per day for 10 days)\textsuperscript{17}. The estimated dose of imatinib loaded on our NP-eluting stent was 21±8 μg/stent, which is markedly lower than the doses used in these prior studies; therefore, it is likely that the inhibition of in-stent neointima formation is mediated by slower release and longer retention of imatinib at the imatinib-NP-eluting stent site in this porcine coronary artery model. To confirm this hypothesis, we tried to measure local tissue concentrations of imatinib immediately after and 6 hours after deployment of a imatinib-NP-eluting stent by the HPLC system as a preliminary experiment, which was under the limit of detection (1 ng/mL). Local concentrations of imatinib after deployment of imatinib-NP-eluting stent are unclear; however, our present data (Fig. 5) demonstrated that the attenuation of in-stent neointima formation by an imatinib-NP-eluting stent was associated with inhibition of the downstream signal of PDGF receptor (ERK) \textit{in vivo}. Therefore, our present data provide evidence that PDGF receptor signaling blockade by an imatinib-NP-eluting stent may be a promising means for preventing in-stent neointima formation \textit{in vivo}.

An impaired arterial healing process has been demonstrated to be a major histopathological feature in arteries exposed to currently marketed DES in experimental animals\textsuperscript{29, 30} and in humans\textsuperscript{4-6}. In this study, neither FITC- nor imatinib-NP-eluting stents had apparent effects on inflammation, injury, and re-endothelialization in porcine coronary arteries \textit{in vivo}, suggesting that this NP-eluting stent system may not impair the healing process and endothelial regeneration in this model. Collectively, these data on vascular compatibility support the notion that this bioabsorbable PLGA NP-eluting stent system could be applied to human subjects. One limitation of this interpretation is that we did not compare delayed endothelial healing effects between our NP-eluting stent and current DES devices. In this respect, we do not know whether this approach may have an advantage over currently marketed first-generation DES devices. Future studies are needed to prove this point. Another limitation is that this study was performed in normal pigs without pre-existing atherosclerotic coronary lesions, although this porcine coronary artery model is regarded as an appropriate and standard preclinical study model\textsuperscript{31}. A long-term efficacy study is also needed.

We and others have reported that monocyte-mediated inflammation induced by monocyte chemoattractant protein-1 (MCP-1) plays a central role in the pathogenesis of neointima formation\textsuperscript{24, 32-36} and in atherogenesis\textsuperscript{37, 38}. If imatinib and anti-MCP treatment exert their effects through different pathways, it would be interesting to examine whether combined...
blockade of PDGF-R and MCP-1 would have additive inhibitory effects on in-stent stenosis.

In conclusion, blockade of PDGF signaling by imatinib-NP inhibited the proliferation of VSMC with no adverse effects on endothelial cells in vitro, and an imatinib-NP-eluting stent attenuated in-stent neointimal formation in porcine coronary arteries in vivo. This molecular-targeting NP-eluting stent system may be an innovative platform for delivering agents that target future diagnosis and treatment of atherosclerotic vascular disease.

Funding Sources

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Disclosures

Dr. Egashira hold a patent on the results reported in the present study. The remaining authors report no conflicts.

References


34) Egashira K: Molecular mechanisms mediating inflammation in vascular disease: Special reference to monocyte chemoattractant protein-1. Hypertension, 2003; 41: 834-841


