Shiga-Like Toxin II Derived from Escherichia coli O157:H7 Modifies Renal Handling of Levoﬂoxacin in Rats

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The effect of Shiga-like toxin II (SLT-II) (2 µg/animal), which was derived from Escherichia coli O157:H7, on renal handling of levoﬂoxacin (LVX), a model drug for quinolone antimicrobial agents, was investigated in rats 24 h after intravenous injection. In histopathological examination, acute tubular injury was observed in SLT-II-treated rats, but the glomeruli were not injured. SLT-II signiﬁcantly increased the steady-state concentration of LVX in plasma to 1.5-fold that of control rats. SLT-II induced signiﬁcant decreases in the glomerular ﬁltration rate (GFR) and renal clearance (CLR) of LVX. SLT-II slightly, but signiﬁcantly, increased the unbound fraction and decreased renal plasma ﬂow with no change in the extraction ratio of p-aminophenipurn. SLT-II signiﬁcantly increased concentrations of tumor necrosis factor alpha (TNF-α) and nitrite and nitrate (NOx) in plasma. The TNF-α inhibitor pentoxifylline partly, but signiﬁcantly, inhibited SLT-II-induced decreases in the GFR and CLR of LVX; in contrast, s-methylisothiourea, a selective inhibitor of inducible nitric oxide synthase, did not. Western blotting analysis revealed that SLT-II did not alter the levels of multidrug resistance-associated protein 2 (Mrp2) and P-glycoprotein in kidneys 24 h after injection, assuming the lack of involvement of Mrp2 and P-glycoprotein in SLT-II-induced acute renal tubular injury and renal handling of LVX observed 24 h after SLT-II injection. The present study suggests that SLT-II impairs the renal handling of LVX by decreasing GFR and causing decreased renal plasma ﬂow.

It is well-known that drug disposition is altered in some disease states, notably those associated with functional changes in the kidney, which plays a crucial role in drug and metabolite excretion. We have extensively studied changes in the renal excretion of organic anion drugs in cases of renal failure and insufﬁciency associated with various disease states, especially endotoxemia induced by a gram-negative bacterial infection (2, 9, 20–23, 37).

Escherichia coli O157:H7 infection induces colonization of the bowel and production of powerful Shiga-like toxins (SLTs), which are thought to enter the circulation system and to cause injury to target endothelial cells in various organs, such as the renal glomeruli and the gastrointestinal tract. The SLTs can be divided into two major types: SLT type I (SLT-I) and type II (SLT-II) (16, 24). SLT-II is known to induce nonspeciﬁc diarrhea, hemorrhagic colitis, and severe hemolytic-uremic syndrome (HUS). In particular, HUS is the most serious complication of E. coli O157:H7 infection and contributes to renal dysfunction and mortality. However, what and how therapy with antimicrobial agents should be done in the treatment of this infection has not yet been clinically clariﬁed. Relevant animal models for E. coli O157:H7 infection are needed to study the physiological and pathological states of E. coli O157:H7 infectious disease in humans because of the difﬁculties associated with conducting clinical trials with humans. A wide variety of animal species, such as rabbits, dogs, and mice, have been used as models for human E. coli O157:H7 infections (3, 8, 10). For example, it has been reported that SLT-II isolated from E. coli O157:H7 induces colonic mucosal necrosis and hemorrhage, renal tubular necrosis, and lymphoid necrosis in various tissues in mice (4, 25). In one study, rats were used as an animal model of HUS and hemorrhagic colitis by intravenous injection of SLT-I derived from E. coli O157 (19).

New quinolone antimicrobial agents are sometimes used for the treatment of E. coli O157 infection in Japan. Of the new quinolones, levoﬂoxacin (LVX) has been shown to improve overall mortality of mice infected by E. coli O157:H7 (13). LVX is mainly excreted into the urine by active tubular secretion by drug transporters (38). It has been suggested that LVX is transported by P-glycoprotein (14, 39) and the multispeciﬁc organic anion transporter multidrug resistance-associated protein 2 (Mrp2) (27, 28, 34). Therefore, SLT-II might modify the renal handling of LVX by inducing histopathological and physiological changes in kidneys and/or by impairing both drug transporters (Mrp2 and P-glycoprotein). However, the roles of SLT-II in kidney function, renal handling of new quinolone antimicrobial agents, and drug transport systems in humans and animals have not yet been elucidated.

We designed a series of experiments to develop guidelines for the safe use of quinolone antimicrobial agents. We examined the effects of SLT-II on the renal handling of LVX as a...
model drug for quinolone antimicrobial agents that are excreted mainly into urine and the expression of Mrp2 and P-glycoprotein in the kidney.

**MATERIALS AND METHODS**

**Chemicals.** LVX was a kind gift from Daiichi Pharmaceutical Co., Ltd. (To-kyo, Japan). 5-Methylthiourica (SMT), pentoxifylline (PTX), and p-aminophen-ypurine (PAP) were purchased from Sigma Chemical Co. (St. Louis, Mo.). Insulin was purchased from Nacalai Tesque (Kyoto, Japan). Grepafloxacin, which was used as an internal standard, was a kind gift from Otsuka Pharmaceutical Co., Ltd. (Osaka, Japan). All other reagents are commercially available and were of analytical grade.

**Preparation of SLT-II.** The clinically isolated *E. coli* O157:H7 strain NGY12 was used for the production of SLT-II. This strain does not produce SLT-I. The absence of the 6b gene was confirmed by PCR with specific primers. The strain was grown in 500 ml of Luria broth (LB) by constant shaking for 12 h at 37°C. The culture supernatant was obtained by centrifugation, and the protein fraction was precipitated with 60% saturated ammonium sulfate at 4°C. The precipitate was collected by centrifugation, dissolved in 2 ml of phosphate-buffered saline (PBS) (pH 7.2), and dialyzed overnight against PBS at 4°C. The diacyl (approx. 2.5 mg/ml) was used as the crude SLT-I preparation. The concentration of SLT-II in the crude preparation was 20 μg/ml, which was determined by using a reverse passive latex agglutination kit (VTEC-RPLA; Denka Seiken Co., To-kyo, Japan).

**Animal experiments.** Male Wistar rats (Nippon SLC, Hamamatsu, Japan), weighing 290 to 300 g, were used in this study. The rats were housed under controlled environmental conditions (temperature of 23°C ± 1°C and humidity of 55% ± 5%) with a commercial food diet and water freely available to the animals. All animal experiments were performed according to the guidelines of the Nagoya University School of Medicine for the care and use of laboratory animals.

To determine the effect of SLT-II on the concentration-time curve of LVX in plasma, one day before the experiments, rats were anesthetized with sodium pentobarbital (25 mg/kg of body weight) and the right jugular vein of each rat was cannulated with a polyethylene tube for injection of SLT-II or saline. Twenty-four hours after the intravenous injection of SLT-II (2 μg/animal) or saline, the rats received a single intravenous injection of LVX (10 mg/kg). Blood samples were collected at designated intervals after the injection of LVX. Plasma samples obtained by centrifugation were stored at −40°C until analysis.

To elucidate the effect of SLT-II on renal handling of LVX, 24 h after intravenous injection of SLT-II (2 μg/animal) or saline, the rats (under light anesthesia with pentobarbital) were cannulated with polyethylene tubes into the left jugular arterial and the urinary bladder for the collection of blood and urine samples, respectively. All the experiments were performed by placing the rats under anesthesia with pentobarbital, and the body temperatures of the animals were maintained at 37°C with a heat lamp. The rats received a bolus intravenous injection of LVX and insulin in a loading dose of 1.5 and 25 mg/kg, respectively, followed by a constant-rate infusion, using an infusion pump (PHD 2000; Har-vard Company, South Natick, Mass.), of a 4% mannitol solution delivering doses maintained at 37°C and humidity of 55% with a commercial food diet and water freely available to the rats (both sets of rats were lightly anesthesized with ethyl ether), and plasma samples were immediately obtained by centrifugation. Four hundred microliters of a PBS solution (pH 7.4) containing 1 μg of LVX per ml was dialedyzed against an equal volume of a fresh plasma sample at 37°C for 8 h to attain equilibrium. Concentrations of LVX on both sides of the membrane were measured by high-perfor-mance liquid chromatography (HPLC).

**Drug analysis.** Concentrations of LVX and PAH in plasma and urine were determined by HPLC. Urine samples were diluted in distilled water. The assay for PAH was performed by a modified version of the method reported previously (1). Fifty microliters of each sample and either 200 μl of methanol containing grepafloxacin (0.1 μg/ml) for LVX or 300 μl of acetaminol containing 1-p-sulfamoylbenzoic acid (3 μg/ml) for PAH as internal standards were mixed and centrifuged at 12,000 × g for 5 min. After centrifugation, the supernatant (200 μl) was then dried under a stream of nitrogen gas at 40°C. The residue was reconstituted in the mobile phase and subjected to HPLC. The LC-6A system (Shimadzu, Kyoto, Japan), equipped with a fluorescence detector (model RF-535; Shimadzu) (emission wavelength, 505 nm; excitation wavelength, 330 nm), or an SPD-6A UV spectrophotometric detector (operated at 254 nm), consisting of an LC-6A liquid pump and an SIL-6A autoinjector, was used for HPLC. HPLC was performed with the following equipment and conditions: Cosmosil SCX columns (4.6 by 150 mm; Nacalai Tesque); mobile phase for LVX, 20 mM Na 2SO 4 –acetonic acid (80:20 [vol/vol]) solution containing 0.1% H 3PO 4; mobile phase for PAH, 50 mM NaHPO 4 containing 0.5 mM tetrabutyl ammonium hydrogen sulfate–methanol (90:10 [vol/vol]); column temperature (OTC-6A: Shimadzu); 40°C for LVX and 50°C for PAH, and flow rate, 1.0 ml/min for LVX and 0.6 ml/min for PAH. These assays were shown to be linear for the concentrations studied with a correlation coefficient of 0.999. No interference with the peak of LVX or PAH was observed in any samples. The within-day and between-days coefficients of variation for this assay were less than 8%. Plasma inulin concentration was measured by the standard colorimetric method (7).

**Data analysis.** For the renal handling experiments of LVX, the renal clearance (CLR) of LVX, inulin, and PAH during each urine sample collection period was calculated by dividing the urinary excretion rate by the steady-state plasma drug concentration (C SS) determined for that collection period. The renal clearance of drug not bound to plasma protein (CLR RU) was calculated by dividing CLR by the plasma-unbound fraction (f U). Glomerular filtration rate (GFR) was calcu-lated as inulin clearance. Assuming that the renal tubular reabsorption of LVX is negligible, the tubular secretion clearance of unbound drug (CLS) was calcu-lated as CLR − CLR RU. Each parameter was calculated by using the mean value for three datum points during 60 min.

RPF was calculated as RPF = CLR,RU (ER), where CLR,RU (ER) is the renal clearance of PAH, respectively. The ER of PAH was calculated as ER = (C PAH − C RPAH)/C PAH.
where \(C_{in}\) and \(C_{out}\) are the concentrations of PAH entering (carotid artery) and leaving (renal vein) the kidney at the same time point.

**Western blot analysis.** Kidneys were obtained from control rats and rats treated 12, 24, and 48 h earlier with SLT-II. Each kidney was suspended in 1 ml of 10 mM Tris-HCl buffer (pH 8.0) containing complete protease inhibitor, 1.5 \(\mu\)g of aprotinin per ml, and 1 mM phenylmethylsulfonyl fluoride (Sigma Chemicals). The suspension was homogenized with a tight homogenizer (20 strokes up and down) and centrifuged at 2,000 \(\times\) g for 15 min at 4°C. The supernatant was centrifuged at 30,000 \(\times\) g for 60 min at 4°C. The pellet was dissolved in Laemmli buffer and incubated at 37°C for 15 min.

The protein concentration in the solution was measured by Bio-Rad Protein Assay (Bio-Rad Laboratories, Richmond, Calif.) using bovine serum albumin (Sigma Chemicals) as a standard. The protein (40 \(\mu\)g) was separated by electrophoresis on a sodium dodecyl sulfate–8% polyacrylamide gel and transferred to a nitrocellulose membrane. The membrane was blocked in PBS containing 0.1% Tween 20 and 5% nonfat dry milk, detected by C219 mouse monoclonal antibody to Mrp2 (Alexis Biochemicals, San Diego, Calif.). To quantify the relative levels of P-glycoprotein in each gel, the intensity of the stained bands was measured by NIH image (National Institutes of Health, Bethesda, Md.). To determine the effect of SLT-II on the renal handling of LVX, we performed in vivo clearance experiments with the continuous infusion method. The parameters for the renal handling of LVX in the control and SLT-II-treated rats are summarized in Table 1. The steady-state concentrations of LVX in plasma (\(C_{ss}\)) in SLT-II-treated rats were significantly higher than those in control rats (0.77 ± 0.11 and 0.49 ± 0.08 \(\mu\)g/ml, respectively). The GFR and \(CL_R\) of LVX dropped to 50% in SLT-II-treated rats (2.84 to 1.43 ml/min and 4.13 to 2.19 ml/min, respectively). SLT-II significantly decreased albumin concentration in plasma (3.62 to 3.15%) and increased the \(f_u\) of LVX (0.84 to 0.87). To exclude the effect of plasma protein binding on the renal excretion of LVX, renal clearance for unbound drug (\(CL_{R,U}\)) was calculated. As a result, the value of \(CL_{R,U}\) for LVX in SLT-II-treated rats significantly decreased by approximately 50%. Then, assuming that the renal tubular reabsorption of LVX is negligible, the net tubular secretion clearance (\(CL_S\)) of LVX was decreased in SLT-II-treated rats.

As the renal handling experiments showed that SLT-II decreased the GFR and \(CL_S\) of LVX, we examined the effects of SLT-II on RPF and PAH. As shown in Table 2, SLT-II significantly decreased renal clearance of PAH (9.09 to 6.54 ml/min) and RPF (11.23 to 8.08 ml/min). However, there was no significant difference in the ER for the control and SLT-II-treated rats.

To investigate the roles of TNF-\(\alpha\) and NO in SLT-II-induced reduction in the renal excretion of LVX and in the GFR, the protective effects of PTX (a nonselective inhibitor of TNF-\(\alpha\) production) and SMT (an iNOS inhibitor) against SLT-II-induced reduction of the GFR and \(CL_S\) of LVX were de-
We also measured levels of TNF-α and NOx in plasma after intravenous injection of SLT-II. Concentration-time curves of TNF-α and NOx in plasma after injection of SLT-II are shown in Fig. 3. The concentration of TNF-α peaked at approximately 1.5 h after injection of SLT-II (approximately 1,500 pg/ml), whereas the concentration of NOx in plasma started to increase 4 to 6 h after injection of SLT-II and peaked at approximately 12 h (approximately 800 μM). The inhibitory effects of PTX and SMT against SLT-II-induced decreases in the GFR and CLR of LVX are illustrated in Fig. 4. PTX significantly inhibited the effect of SLT-II on the GFR and CL_R of LVX, but the inhibition was incomplete. On the other hand, SMT had no protective effect against SLT-II-induced decreases in the GFR and CL_R of LVX.

We investigated the effects of SLT-II on the levels of Mrp2 protein and P-glycoprotein in kidney tissue by Western blotting. Figure 5 depicts changes in the levels of Mrp2 and P-glycoprotein as a function of SLT-II. As shown in Fig. 5, SLT-II did not alter the protein level of Mrp2 in the kidney for 48 h after injection. The level of P-glycoprotein remained unchanged for 24 h but decreased to 70% of the control level after 48 h.

DISCUSSION

For HUS patients, it has been reported that glomerular endothelial cells are swollen and detached from the glomerular basement membrane and that glomerular capillaries are occluded with microthrombi (26). In this study using rats, SLT-II induced acute tubular epithelial cell injury without glomerular damage. These results are in accordance with findings by Wadolkowski and colleagues (35, 36), who reported that SLT-II-producing E. coli induced acute renal tubular necrosis in mice, but not glomerular damage. Tesh et al. (32) also reported that SLT-II-induced acute renal tubular necrosis was the only histological lesion in mice. It is likely that the rat model is similar to the mouse model, but the pathological lesions in the kidneys differ from those observed in HUS patients. The differences may be caused by tissue-specific differences in the distribution and expression of globotriosylceramide (Gb₃), which is a functional receptor for SLTs.

In the present study, a significant delay in the disappearance of LVX from plasma was observed in SLT-II-treated rats, indicating that SLT-II delays the elimination of LVX from the body. Considering that LVX is excreted primarily into urine and that the protein binding of LVX was very weak (approximately 15%), SLT-II might decrease the renal excretion of LVX. The renal handling experiments clearly showed that in SLT-II-treated rats, the GFR and CL_R of LVX decreased by approximately 50% from the values for the control rats. The clearance ratio (CL_R/LVX) of LVX in control rats was approximately 1.8, suggesting that LVX is actively secreted into urine by certain drug transporters. The present study also found that SLT-II decreased RPF. These results suggest that

<table>
<thead>
<tr>
<th>Group</th>
<th>GFR (ml/min)</th>
<th>CL_R (ml/min)</th>
<th>CL澳大 (ml/min)</th>
<th>CLS (ml/min)</th>
<th>Albumin concn (%)</th>
<th>fU</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLT-II treated</td>
<td>1.43 ± 0.35</td>
<td>2.19 ± 0.39</td>
<td>2.51 ± 0.44</td>
<td>1.07 ± 0.45</td>
<td>3.15 ± 0.24</td>
<td>0.87 ± 0.01</td>
</tr>
<tr>
<td>Control</td>
<td>2.84 ± 0.38</td>
<td>4.13 ± 1.08</td>
<td>5.10 ± 1.33</td>
<td>2.25 ± 1.02</td>
<td>3.62 ± 0.10</td>
<td>0.84 ± 0.01</td>
</tr>
</tbody>
</table>

a Values are means ± standard deviations (n = 5 to 6). Significant differences were observed for all parameters in the control and SLT-II-treated groups (P < 0.05).
the SLT-II-induced decrease in the CL_{R} of LVX is caused by reduction of GFR and/or tubular secretion. However, the renal ER of PAH did not change, despite renal tubular cell damage. The precise cause cannot be explained at this stage, although tubular cell damage may be moderate. On the basis of these findings, it is presumed that SLT-II-induced decreases in the GFR and CL_{R} of LVX may be partially caused by the decrease in RPF.

Organic anion transporter 1 (OAT1), recently isolated from rat kidney (29, 30), may be one of the multispecific organic anion transporters related to the excretion of anion drugs from the kidney. It has been reported that PAH, but not new quinolone antimicrobial agents, are substrates for OAT1 (15, 29) and that PAH had no inhibitory effect on the uptake of LVX in rat renal cortical slices (14). These observations suggest the lack of involvement of the OAT1-mediated transport system to the renal excretion of LVX.

We recently found that a newly developed quinolone antimicrobial agent, grepafloxacin, is excreted into bile by a P-glycoprotein-mediated transport mechanism (39). Ito and colleagues (14) reported that quinidine, a typical substrate for P-glycoprotein, inhibited the uptake of LVX in rat kidney slices. Thus, it is likely that LVX is a substrate for P-glycoprotein. On the other hand, it has been reported that quinolone antimicrobial agents are substrates for the multispecific organic anion transporter Mrp2 (27, 28, 34).

It is generally thought that renal failure causes the suppression of drug transporter function. We investigated whether SLT-II could reduce the levels of Mrp2 protein and P-glycoprotein related to renal excretion of LVX by Western blotting. However, the levels of expression of Mrp2 and P-glycoprotein cannot explain SLT-II-induced decreases in the CL_{R} and CL_{S} of LVX. It has been reported that plasma samples obtained from rats with acute renal failure inhibit P-glycoprotein-mediated transport system (11), suggesting the presence of endogenous P-glycoprotein substrates in plasma in rats with acute renal failure. One possible explanation may be that endogenous substances or putative Mrp2 and P-glycoprotein substrates in the body inhibit the renal excretion of LVX by modulating Mrp2 and P-glycoprotein transporters because renal failure causes the accumulation of such substances in the body (5, 12, 31). On the basis of these observations, it is suggested that a SLT-II-induced decrease in the CL_{S} of LVX is caused, at least in part, by decreasing RPF and accumulating putative Mrp2 and P-glycoprotein substrates in the body. Consequently, we assume that the unchanged levels of Mrp2 protein and P-glycoprotein in the kidney 24 h after injection of SLT-II play a protective function against SLT-II-induced damage to the kidney by serving to excrete endogenous toxic substances into urine. However, further studies are needed to clarify the existence of other renal transporters responsible for LVX excretion.

There is evidence that SLT-I and SLT-II induce expression of proinflammatory cytokines (33) and that the cytokines interleukin 1 and TNF-α up-regulate the expression of the toxin-binding neutral glycolipid Gb₃ receptor in endothelial cells (17), suggesting that cytokines may play a role in SLT-II-

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**TABLE 2. Effects of SLT-II on RPF and ER of PAH**

<table>
<thead>
<tr>
<th>Group</th>
<th>CL\textsubscript{PAH} (ml/min)</th>
<th>ER</th>
<th>RPF (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLT-II treated</td>
<td>6.54 ± 0.06\textsuperscript{a}</td>
<td>0.81 ± 0.05</td>
<td>8.08 ± 0.44\textsuperscript{a}</td>
</tr>
<tr>
<td>Control</td>
<td>9.09 ± 1.18</td>
<td>0.81 ± 0.08</td>
<td>11.23 ± 1.34</td>
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</tbody>
</table>

\textsuperscript{a} Values are means ± standard deviations (n = 3). 
\textsuperscript{b} Significantly different from the value for the control group (P < 0.05).

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**FIG. 3.** Concentration-time curves of TNF-α and NOx in plasma after intravenous injection of SLT-II. Values are shown as means ± standard deviations (error bars) (n = 3).
induced histopathological lesions. It is also known that TNF-α increases NO, which causes tissue damage and excess vasodilation, by inducing iNOS. However, the roles of both the cytokine and mediator in the physiological and pathological changes induced by SLT-II have not yet been fully elucidated. Our previous studies have found that hepatic drug-metabolizing enzyme activity was decreased by SLT-II-induced overproduction of NO in plasma and that a selective iNOS inhibitor, SMT, partly protected the decrease by inhibiting the overproduction of NO (unpublished data). However, this study showed that SMT did not protect SLT-II-induced decreases in the GFR and CLR of LVX. Thus, it is unlikely that the expression of both the cytoprotective cytokine and protection by SMT is related to the overproduction of NO in the plasma.

FIG. 4. Protective effects of PTX and SMT against SLT-II-induced decreases in the GFR and CLR of LVX. Means ± standard deviations (error bars) are shown (n = 5). Values that are significantly different from those of the control and SLT-II-treated rats (P < 0.05) are indicated by the letters a and b, respectively.

FIG. 5. P-glycoprotein (A) and Mrp2 (B) expression in the kidneys of rats treated with SLT-II or not treated with SLT-II (control) (top) and relative staining intensity for Mrp2 and P-glycoprotein in control and SLT-II-treated rats (bottom). Kidney samples were taken 12, 24, and 48 h after intravenous injection of SLT-II (2 μg/animal). Each bar represents the intensity ratio compared to the value for the control rats and is presented as the mean ± standard deviation (error bar) (n = 3). The value that is significantly different from the control value (P < 0.05) is indicated by the letter a.
of iNOS or overproduction of NO plays a key role in SLT-II-induced kidney dysfunction. We recently reported that pre-treatment with PTX significantly inhibited endotoxin-induced increases in TNF-α levels in plasma (2). In the present study, PTX partly ameliorated SLT-II-induced renal failure and reduction of CL_κ of LVX, suggesting that TNF-α is weakly related to SLT-II-induced renal failure.

In conclusion, the present study is the first to report that SLT-II decreases the renal excretion of LVX by decreasing GFR and RPF and induces renal tubular necrosis but has no effect on the levels of Mrp2 protein and P-glycoprotein in the kidney 24 h after injection. The levels of Mrp2 protein and P-glycoprotein could not explain decreased renal excretion of LVX by SLT-II. This phenomenon is probably due to accumulation of endogenous toxic substances and/or putative substrates for Mrp2 and P-glycoprotein in plasma and in the kidney. It is also likely that TNF-α and NO do not play major roles in SLT-II-induced renal tubular damage. However, further studies will be needed to identify the transporters that play crucial roles in the renal handling of quinolone antimicrobial agents.

REFERENCES


