Research Article

Pharmacokinetic Actions of Exendin-4 in the Rat: Comparison With Glucagon-Like Peptide-1

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ABSTRACT

Exendin-4, originally isolated from saliva of the lizard Heloderma suspectum, shares 53% sequence homology and several potentially antidiabetic actions with the mammalian hormone glucagon-like peptide-1(7-36)amide (GLP-1). It shows a higher potency and longer duration of effect in vivo, which may be partly attributed to pharmacokinetic properties. The present study compares the pharmacokinetics of GLP-1 and exendin-4 in rats after intravenous (iv), subcutaneous (sc), or intraperitoneal (ip) administration. Samples were assayed for active GLP-1 (7-36) amide using an enzyme-linked immunosorbent assay that does not detect GLP-1 (1-36-amide), (1-37), (9-36-amide) or (9-37). In parallel experiments, samples were assayed for exendin-4 using a two-site immunoradiometric assay that reacts specifically with full-length exendin-4. The estimated half-life for GLP-1 and exendin-4 were 0.8–4.7 min and 18–41 min for iv bolus, and 4.6–7.1 min and 90–216 min for SC administration, respectively. Half-lives after ip injection were 0.6–13.5 min for GLP-1 and 125–174 min for exendin-4. Bioavailability for GLP-1 and exendin-4 was 36–67% and 74–76%, respectively, for sc injection. For ip injection, bioavailability for GLP-1 and exendin-4 was 44–71% and 65–75%, respectively, for sc injection. For ip injection, bioavailability for GLP-1 and exendin-4 was 36–67% and 74–76%, respectively. Plasma clearance, as determined from iv infusion data, was 35–38 ml/min for GLP-1 and 4–8 ml/min for exendin-4. Both Co/Cmax and AUC values were proportional to dose with each route of administration. Plasma clearance of exendin-4 was reduced by 4.4-fold in nephrectomized animals. In conclusion, exendin-4 exhibited a much longer plasma half-life than GLP-1 in rats after iv, sc, or ip injection, which may contribute in some part to reported differences in duration of biological action of the two peptides. Drug Dev. Res. 53:260–267, 2001. © 2001 Wiley-Liss, Inc.

Key words: kinetics; intravenous administration; subcutaneous administration; peptide

INTRODUCTION

Exendin-4 is a 39 amino acid peptide isolated from the salivary secretions of the Gila monster lizard Heloderma suspectum [Eng, 1992]. Exendin-4 shares approximately 53% sequence homology with mammalian GLP-1 [Goke et al., 1993] and can bind to and activate mammalian GLP-1 receptors in in vitro preparations [Thorens et al., 1993; Fehmann et al., 1994; Goke et al., 1993; Schepp et al., 1994; Eissele et al., 1994]. Exendin-4 was discovered to have actions similar to those previously reported for GLP-1, including slowing of gastric emptying [Wettergren et al., 1993; Young et al., 1996; Nauck et al., 1997], reduction in postprandial glucose levels [Koltermann et al., 1999; Fineman et al., 2000], and stimulation of insulin release during states of elevated blood glucose [Egan et al., 1999]. Exendin-4 has also been shown to potently reduce plasma glucose in several diabetic animal models [Gedulin et al., 1998; Young et al., 1999], and is being explored as a therapy for diabetic patients.

Exogenous exendin-4 has been shown to have a
markedly extended duration of action on several biological systems, including its action to lower blood glucose, when compared to GLP-1 [Young et al., 1999]. Hence, the present study investigated the pharmacokinetic properties of both exendin-4 and GLP-1 in anesthetized rats, after intravenous, subcutaneous, or intraperitoneal administration. To assess the involvement of the kidneys in clearance of exendin-4 from blood, we additionally examined the pharmacokinetic profile of intravenously infused exendin-4 in functionally nephrectomized animals. Preliminary data from this study have been published in abstract form [Parkes et al., 2000].

METHODS

Animals

Male Sprague-Dawley (HSD) fasted (18 h) rats (Harlan, Indianapolis, IN), weighing 350–370 g, were housed at 23 ± 1°C in a 12:12-h light:dark cycle, and were given access to food (except as noted) and water ad libitum (Diet LM-485, Teklad, Madison, WI). Anesthesia was induced with 5% halothane and maintained at 2% during surgery and 1–1.5% thereafter. Tracheotomy and cannulation of the right saphenous vein for intravenous infusion/injection, and of the right femoral artery for sampling analytes and for recording arterial pressure was performed. Heparinized saline (2 U/ml) was infused via the arterial line at an infusion rate of 3–4.5 ml/h from t = –1 h. Mean arterial pressure was monitored via the arterial line (Spectramed P23XL transducer, 13-4615-58 Universal amplifier, Gould, Valley View, OH). Colonic temperature was measured and controlled using a thermistor probe/controller (YSI model 73A, Yellow Springs, OH).

In a parallel experiment, three HSD rats were functionally nephrectomized by acute ligation of the renal arteries and veins, and three rats were sham-operated by a similar procedure except that instead of ligation, loose ties were placed around the renal arteries and veins. Exendin-4 was continuously infused intravenously (iv) for 150 min at 5 nmol/h.

All experiments were carried out in accordance with the Guide for Care and Use of Laboratory Animals as adopted and promulgated by the U.S. National Institutes of Health.

Pharmacokinetic Studies

In these rats, Exendin-4 (1-39) or GLP-1-(7-36)-amide was injected via three different routes—intravenous bolus (iv), 3-h continuous intravenous infusion (ivc), subcutaneous (sc) bolus, and intraperitoneal (ip) bolus—at four different doses: 0.05, 0.5, 5, and 50 nmol (bolus injection), and at 0.05, 0.5, 5, and 50 nmol/h (3-h iv infusion). Samples were collected at the time intervals indicated in Figs. 1–5, where 250 μl arterial blood was taken into heparinized Natelson capillaries, the plasma separated on a bench-top centrifuge and then frozen at –20°C until assay. Protease inhibitors were added to blood samples collected for GLP-1 measurement, and the GLP-1 assay was validated for sample stability.

Exendin-4 Immunoradiometric Assay

Samples were assayed using a two-site sandwich assay developed at Amylin Pharmaceuticals, Inc. [Wasada et al., 1999]. The assay used gamma radiation detection in Immulon II microtiter wells (Dynatech, Chantilly, VA) that were coated with monoclonal antibody EXE4:2-8 by overnight incubation at 4°C with 10 mg antibody per ml in 50 mM carbonate buffer, pH 9.6. After incubation, plates were washed with phosphate-buffered saline (PBS)/Tween (0.05 M sodium phosphate, 0.15 M sodium chloride, 0.02% sodium azide, 0.1% Tween 20), blocked with 1% nonfat milk in carbonate buffer for 1 h at room temperature. Specimens, controls, or standards (50 μl) were then added to the plates and incubated for 1 h at

![Fig. 1. Plasma concentrations of exendin-4 or GLP-1 after intravenous bolus in anesthetized rats (n = 4–7). Values are shown as mean ± s.e.m., and doses are in nmol/rat.](image-url)
room temperature. After washing, 150,000 cpm/well of
$^{125}$I-labeled monoclonal detection antibody, GLP1:3-3,
was added. Iodinations were performed using the
chloramine T method, to a specific activity target of 9
µCi/µg. After a 1-h incubation at room temperature, wells
were washed to remove unbound detection antibody.
Radioactivity was detected in an LKB/Wallac Model 1277
gamma counter, and data were analyzed with RIAcalc
software (Wallac, Gaithersburg, MD) using the spline
smoothed fit option. Concentrations of exendin-4 in
plasma specimens were then determined by comparison
with a calibration curve run with the same assay. The
minimum detectable concentration of exendin-4 was 15
pM. Intraassay coefficient of variation was 3.8–0.8%
and interassay coefficient of variation was 7.5–2.2%. The
exendin-4 immunoradiometric assay (IRMA) detects full-
length exendin-4, but not GLP-1 or tested metabolites of
exendin-4 or GLP-1.

**GLP-1 Enzyme-Linked Immunosorbent Assay**

Samples were assayed for full-length active GLP-1
using an assay developed at Linco Research Inc. in col-
laboration with Amylin Pharmaceuticals, Inc. (Linco, Kit
No. EGLP-35K). Microtiter plates (Dynatech) were
coated with anti-GLP-1 monoclonal antibody by over-
night incubation at 4°C. The GLP-1 antibody binds spe-
cifically to the N-terminal region of the active GLP-1
(7-36) amide molecule. Cross-reactivity to GLP-1 (7-36)
amide and GLP-1 (7-36) acid was 100%, but for the princi-
pal metabolite GLP-1 (9-36) amide, and for GLP-2 and
glucagon, cross-reactivity was below the minimum de-
tectable concentration (0.5 pM). Plates were washed with
PBS/Tween20. Samples were thawed on ice and, if nec-
essary, diluted in assay buffer containing 0.05 M PBS pH
6.8, protease inhibitors, Tween 20, 0.08% sodium azide,
and 1% bovine serum albumin. Standards and controls
used the same diluent. Samples (100 µL) and GLP-1 stan-

![Fig. 2. Plasma concentrations during continuous intravenous infusion of exendin-4 or GLP-1 into anesthetized rats for 3 h (t = 0 to t = 3 h) (n = 4–6). Values are shown as mean ± s.e.m., and doses are in nmol/h/rat.](image1)

![Fig. 3. Plasma concentrations of exendin-4 or GLP-1 after subcutaneous bolus in anesthetized rats (n = 4–7). Values are shown as mean ± s.e.m., and doses are in nmol/rat.](image2)
Standards (run in the same assay) were added to the coated plates, covered, and incubated overnight at 4°C. After incubation, plates were decanted and washed in buffer (PBS/Tween20), then incubated in buffer for 5 min at room temperature. Immediately after incubation, the anti-GLP-1 alkaline phosphatase detection conjugate was added to each plate, and incubated for 2 h at room temperature. Bound enzyme was detected by incubation of the plates with the fluorescent substrate 4-methylumbelliferyl phosphate (50 μg/ml) for 30 min at room temperature in the dark. The fluorescent signal was measured with a Dynatech Microfluor plate reader and data analyzed using “Multicale” software (Wallac). The minimum detectable concentration of GLP-1 was 1 pM. Intraassay coefficient of variation was 7.4 ± 0.5% and interassay coefficient of variation was 8.0 ± 1.9%.

**Chemicals and Reagents**

Synthetic exendin-4 (1-39) (Lot no. 97-1210-RP) and GLP-1 (7-36)-amide (Lot no. 1374-25) were made using solid phase methodologies, and shown to be chromatographically pure by high-performance liquid chromatography.

**Data Analysis**

All results are shown as mean ± standard error of the mean (s.e.m.). Limited data are shown for 0.05 nmol doses of exendin-4, because of many plasma samples reading below the lower limit of quantitation for the assay. Data were analyzed for statistical differences by Student’s t-test (Prism, Graphpad Software Inc., San Diego CA). All changes stated within the text are significant to the P < 0.05 level. One- and two-phase pharmacokinetic parameters were calculated by nonlinear, least-squares fit (GraphPad Prism III, GraphPad Software Inc., San Diego, CA). Half-lives were calculated from each respective fit. Other pharmacokinetic parameters (plasma clearance, absolute bioavailability) were calculated from standard equations [Rowland and Tozer, 1989].

**RESULTS**

In general, all routes of peptide administration revealed a dose-dependent effect on plasma concentrations of exendin-4 and GLP-1, when assessed by maximum concentration (Cmax) or integrated time-concentration responses (area under the curve; AUC) (Tables 1 and 2). Bioavailability and clearance rates were independent of dose (Table 3).
The first phase of decay. T½ values for GLP-1 ranged from decayed to within the normal range (1–10 pM) during GLP-1 levels because at most doses, plasma levels had exponential decay model was more appropriate for plasma.

Intravenous Bolus

Plasma exendin-4 and GLP-1 concentrations are plotted as a function of time after iv bolus injection in Figure 1. Exendin-4 doses less than 0.5 nmol generally resulted in plasma concentrations less than the lower limit of quantitation (not included in calculations). Dose-dependent increases in plasma levels (Cmax and C0) were seen with both peptides. When fitted to two-compartment exponential decays, the t½ values for the elimination (β) phase of decay of exendin-4 ranged between 18 and 5 min. A single-compartment exponential decay model was more appropriate for plasma GLP-1 levels because at most doses, plasma levels had decayed to within the normal range (1–10 pM) during the first phase of decay. T½ values for GLP-1 ranged from 0.8 ± 0.1 to 4.6 ± 0.4 min.

Continuous Intravenous Infusion

Plasma concentrations of exendin-4 and GLP-1 during and after infusion rates of 0.05, 0.5, 5, and 50 nmol/h for 3 h are shown in Figure 2. Steady-state plasma concentrations of both peptides were dose dependent. After cessation of infusion, plasma exendin-4 and GLP-1 concentrations decayed at rates similar to those observed after iv bolus injection for each respective peptide. For exendin-4, terminal t½ values ranged from 28 ± 5 to 49 ± 7 minutes, and for GLP-1, t½ values ranged from 0.5 ± 0.2 to 1.2 ± 0.9 min. Plasma clearance rates for exendin-4 during steady-state plasma concentrations ranged from 3.7 ± 0.5 to 8.3 ± 0.7 ml/min, and for GLP-1 from 34 ± 4 to 38 ± 3 ml/min.

Subcutaneous Injection

Figure 3 shows the dose-dependent changes in plasma concentrations of exendin-4 and GLP-1 after sc injection. Exendin-4 plasma levels exhibited a gradual single-phase decay response, commencing approximately 30 minutes (T½) after injection at all doses tested. Kinetics for sc injection of exendin-4 appeared to be absorption-rate limited. In contrast, GLP-1 plasma levels exhibited a rapid single-phase decay immediately after injection equilibrium, where plasma levels rapidly returned to background within 20–60 min of injection. For exendin-4, decay-phase t½ values ranged from 90 ± 3 to 216 ± 13 min, and for GLP-1, t½ values ranged from 4.7 ± 0.8 to 7.1 ± 2.4 min.

### Table 1. Pharmacokinetic Parameters of Exendin-4 and GLP-1 in Anesthetized Rats

<table>
<thead>
<tr>
<th>Route</th>
<th>Exendin-4</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (nmol)</td>
<td>GLP-1</td>
<td>Exendin-4</td>
</tr>
<tr>
<td>0.5</td>
<td>1.04 ± 0.06</td>
<td>1.2 ± 0.4</td>
</tr>
<tr>
<td>5</td>
<td>2.7 ± 0.8</td>
<td>54 ± 12</td>
</tr>
<tr>
<td>50</td>
<td>172 ± 5</td>
<td>763 ± 152</td>
</tr>
</tbody>
</table>

### Table 2. Pharmacokinetic Parameters of Exendin-4 and GLP-1 in Anesthetized Rats

<table>
<thead>
<tr>
<th>Exendin-4</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>iv</td>
</tr>
<tr>
<td>iv Bolus (C0)</td>
<td>0.69 ± 0.08</td>
</tr>
<tr>
<td>5</td>
<td>18 ± 0.9</td>
</tr>
<tr>
<td>50</td>
<td>172 ± 5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>GLP-1</th>
<th>Exendin-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>iv</td>
</tr>
<tr>
<td>iv Bolus (C0)</td>
<td>0.09 ± 0.01</td>
</tr>
<tr>
<td>5</td>
<td>2.5 ± 0.06</td>
</tr>
<tr>
<td>50</td>
<td>2.41 ± 0.20</td>
</tr>
</tbody>
</table>

### Table 3. Pharmacokinetic Parameters of Exendin-4 and GLP-1 in Anesthetized Rats

<table>
<thead>
<tr>
<th>Exendin-4</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (nmol)</td>
<td>civ (ml/min)</td>
</tr>
<tr>
<td>0.5</td>
<td>8.3 ± 0.7</td>
</tr>
<tr>
<td>5</td>
<td>4.8 ± 0.4</td>
</tr>
</tbody>
</table>

### Table 4. Pharmacokinetic Parameters of Exendin-4 and GLP-1 in Anesthetized Rats

<table>
<thead>
<tr>
<th>Exendin-4</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (nmol)</td>
<td>civ (ml/min)</td>
</tr>
<tr>
<td>0.5</td>
<td>35 ± 11</td>
</tr>
<tr>
<td>5</td>
<td>34 ± 4</td>
</tr>
<tr>
<td>50</td>
<td>38 ± 3</td>
</tr>
</tbody>
</table>

*Plasma clearance (Cl) and 6-h absolute bioavailability (B/A) (± s.e.m.) are shown for each appropriate route of administration. Plasma clearance rates were derived from iv infusion data (civ). Bioavailability data are not shown for the 0.5-nmol dose of exendin-4 because several concentration values were less than the lower limit of quantitation for the immunoradiometric assay.
The present study is the first to compare the pharmacokinetic properties of GLP-1 and exendin-4 using sensitive and specific assays, and has shown that exendin-4 exhibits significantly longer plasma half-life than active GLP-1 (7-36) amide after iv, sc, or ip administration in rats. Half-lives for active GLP-1 ranged from 1–13 min across all routes, whereas those for exendin-4 ranged from 18–41 min for iv injection, to more than 2–3 hours with sc or ip injection. All routes of injection showed a dose-dependent increase in maximal concentration and integrated time-concentration profiles (AUC) for both peptides.

The rapid degradation of active GLP-1 in blood by endogenous proteases, specifically dipeptidyl peptidase IV (DPPIV), has been well characterized [Mentlein et al., 1993; Deacon et al., 1995], and contributes significantly to the short half-life reported for GLP-1 in all species studied [Knudsen and Pridal, 1996; Pridal et al., 1996; Deacon et al., 1998; Ritzel et al., 1995]. In fact, the clearance rate of GLP-1 from plasma is up to two times higher than cardiac output in rats. Exendin-4, however, has been shown to be much more stable in plasma and more resistant to degradation by DPPIV in vitro (R. Dilts, unpublished observations). This may contribute to the lower plasma clearance rate for exendin-4 (versus GLP-1) reported in this study, which approximates the glomerular filtration rate in the rat (1 ml/min/100 g body weight) [Flamenbaum et al., 1974]. Further evidence to support renal involvement in clearance of exendin-4 from blood is provided by the pharmacokinetic studies performed here on functionally nephrectomized rats. Plasma concentrations of exendin-4 were markedly elevated versus control rats during iv infusion, and clearance rates from blood were 4.4-fold lower. Furthermore, because levels of exendin-4 had not reached a steady state by 150 min, a time when sham animals were in steady state, this may suggest that the kidneys may play an even more important role in the metabolism of exendin-4 than can be elucidated from the data in this study. A recent study has also suggested that the kidney is indeed involved in the clearance of GLP-1 from blood [Hassan et al., 1999].

Half-lives for subcutaneous and intraperitoneal dosing with exendin-4 were considerably longer than those for intravenous doses, an observation consistent with slow absorption from the site of injection and/or slow rate of degradation at these sites relative to the rate of disappearance from the plasma. With the two highest intravenous doses, the concentration-decay curves were consistent with half-lives of approximately 6–8 min for the α phase and 28–49 min for the β phase at the higher doses. Shorter half-lives were estimated at the lower doses of 0.5 nmol, which produced concentrations near the detection limit of the assay for a number of sampling times. Interestingly, the decay half-lives observed for

### Table 4. Pharmacokinetic Parameters of Exendin-4 and GLP-1 in Anesthetized Rats

<table>
<thead>
<tr>
<th></th>
<th>Exendin-4</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>iv</td>
<td>civ</td>
</tr>
<tr>
<td>Dose (nmol)</td>
<td>α</td>
<td>β</td>
</tr>
<tr>
<td>0.5</td>
<td>3.1±0.4</td>
<td>18±0.5</td>
</tr>
<tr>
<td>5</td>
<td>6.3±1.6</td>
<td>28±1.8</td>
</tr>
<tr>
<td>50</td>
<td>8.4±1.7</td>
<td>41±2.1</td>
</tr>
</tbody>
</table>

αHalf-life is expressed in minutes ± s.e.m. For exendin-4, “α” half-life represents the first (distribution) phase, and “β” half-life represents the second (elimination) phase of decay. civ, continuous iv infusion (3 h).

### Intrapertoneal Injection

Figure 4 shows the dose-dependent changes in plasma concentrations of exendin-4 and GLP-1 after ip injection. Exendin-4 plasma levels exhibited a single-phase decay response, commencing approximately 60 min (T_max) after injection at all doses tested. As with sc dosing, ip kinetics of exendin-4 appeared to be absorption-rate limited. GLP-1 plasma levels exhibited a rapid single-phase decay immediately after injection equilibrium, where plasma levels rapidly returned to background within 30–120 min of injection. For exendin-4, decay phase t_0 values ranged from 125±19 to 174±16 min, and for GLP-1, t_0 values ranged from 0.6±2.0 to 13.5±4.6 min.

### Continuous Intravenous Infusion in Nephrectomized Animals

In a separate experiment, plasma concentration versus time profiles were obtained for exendin-4, after 3-hour iv infusion at a dose of 5 nmol/h in three control rats and three rats with functional nephrectomy (Fig. 5). When exendin-4 was infused iv at 5 nmol/h, plasma exendin-4 concentrations approached a steady-state level of 19±5 nM in control rats, compared to a maximum (non–steady-state) level of 83±39 nM in nephrectomized rats after 150 min. Plasma levels of exendin-4 exhibited a cumulative increase during infusion, in the nephrectomized animals only. After stopping infusion, plasma exendin-4 levels declined in a two-phase decay fashion. The t_0 for terminal decay of exendin-4 in control rats was 67±31 min, but was fivefold higher (326±76 min) in nephrectomized rats. Clearance of exendin-4 was 0.86 ml/min in nephrectomized rats, whereas that in sham-operated control rats was 4.3 ml/min.
GLP-1 were relatively independent of the route of administration. This suggests that kinetics of GLP-1 are not dependent on absorption rate from ip or sc sites of injection, but that the peptide may be rapidly degraded once it enters the circulation.

The limitations of an immunoassay can significantly impact the quality of results of a pharmacokinetic study, and more recently developed assays for GLP-1 have been more specific for active GLP-1 (7-36) amide in addition to exhibiting better sensitivity [Gutniak et al., 1996; Nauck et al., 1997]. Some GLP-1 assays developed more than 3–5 years ago detected fragments of GLP-1 (7-36) amide as well as the intact peptide, giving a measurement of total GLP-1 blood levels including immunoreactive metabolites. The use of a novel, highly specific and sensitive (0.5 pM) assay for active GLP-1 (7-36) amide in the present study has permitted more accurate assessment of true pharmacokinetics for this peptide. The data for exendin-4 in this report were obtained using an IRMA with a lower limit of quantification of approximately 15 pM, so only concentrations considerably higher than this could reliably be used in calculating kinetic data. The specificity of the exendin-4 IRMA for parent (full length) exendin-4 (1-39) has been established [Petrella et al., 1999], and the assay does not detect fragments of exendin-4 (exendin-4 2-39, 3-39, exendin-3) or endogenous peptides of the glucagon family (glucagon, GLP-1 7-36, 9-36, GLP-2). The pharmacokinetic properties of exendin-4 obtained from the present study closely match those reported in a previous study (data not shown), where plasma exendin-4 was determined using a polyclonal antibody-based radioimmunoassay that detected multiple fragments of exendin-4, in addition to the native peptide. Hence, this may suggest that both assays may be detecting similar immunoreactive peptides in plasma, namely, exendin-4 (1-39), and that few degradation products of exendin-4 are present in blood during this period.

In conclusion, we have presented for the first time a detailed comparison of iv, sc, and ip pharmacokinetics of active GLP-1 in rats, and compared this to the kinetics of the structurally related peptide exendin-4. The specificity and sensitivity of these novel immunoassays has enabled accurate determination of plasma kinetics for native/full-length exendin-4 (1-39) and GLP-1 (9-36) amide. The significant differences in clearance rates of GLP-1 and exendin-4 may contribute in part to the reported differences in duration of glucose lowering exhibited by these peptides in animal and human studies.

ACKNOWLEDGMENTS

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REFERENCES


