To find mammalian analogues of exendin-4, a peptide from Helodermatidae venoms that interacts with newly discovered exendin receptors on dispersed acini from guinea pig pancreas, we examined the actions of recent additions to the vasoactive intestinal peptide/glucagon family of regulatory peptides. In every respect tested, the truncated form of glucagon-like peptide-1, GLP-1(7-36)NH₂, mimicked the actions of exendin-4. Like exendin-4, GLP-1(7-36)NH₂ caused an increase in acinar cAMP without stimulating amylase release. GLP-1(7-36)NH₂-induced increases in cAMP were inhibited progressively by increasing concentrations of the specific exendin-receptor antagonist, exendin(9-39)NH₂. In dispersed acini from guinea pig and rat pancreas, concentrations of GLP-1(7-36)NH₂ that stimulated increases in cAMP caused potentiation of cholecystokinin-induced amylase release. Binding of ¹²⁵I-[Y⁹]exendin-4 or ¹²⁵I-GLP-1(7-36)NH₂ to dispersed acini from guinea pig pancreas was inhibited by adding increasing concentrations of unlabeled exendin-4 or GLP-1(7-36)NH₂. We conclude that the mammalian peptide GLP-1(7-36)NH₂ interacts with exendin receptors on dispersed acini from guinea pig pancreas. Exendin(9-39)NH₂, a competitive antagonist of the actions of GLP-1(7-36)NH₂ in pancreatic acini, may be a useful tool for examining the physiological actions of this peptide.

Recently, we reported the isolation, purification, and sequences of two new bioactive peptides, designated exendin-3 (1) and exendin-4 (2), from Helodermatidae venoms. Interaction of these reptilian peptides with newly discovered exendin receptors on dispersed acini from guinea pig pancreas results in an increase in cellular cAMP without stimulation of amylase release (2, 3). Mammalian peptides that are currently known to increase pancreatic acinar cAMP, like vasoactive intestinal peptide (VIP), secretin, peptide histidine isoleucine (PHI), growth hormone-releasing factor, and calcitonin gene-related peptide, do not interact with exendin receptors (3).

In the present study, we sought mammalian peptides that interact with exendin receptors. Our strategy included examination of the biological actions of peptides that are structural analogues of exendin-4 and the use of a specific exendin-receptor antagonist, exendin(9-39)NH₂ (2, 3) as a tool to test for interaction of these peptides with exendin receptors. We focused attention on the following peptides: glucagon-like peptide-1 (GLP-1(1-37) and the truncated form GLP-1(7-36)NH₂), glucagon, GLP-2(1-34), and pituitary adenylyl cyclase-activating peptide (PACAP-38). These peptides share 53, 45, 26, and 18% homology, respectively, with exendin-4 (Fig. 1).

The existence of GLP-1(1-37) and GLP-2(1-34) was suggested by the sequence of the mammalian glucagon gene (4-8). These peptides, and the truncated form of GLP-1, have been reported in rat intestine and pancreatic islets (9-11), pig small intestine and pancreas (12, 13), and in human ileum, pancreas and plasma (14). Glucagon-like effects of the truncated form of GLP-1 lacking the NH₂-terminal 6 amino acids have been observed in several tissues (see Ref. 15, for review). Although it has been reported that GLP-1(7-36)NH₂ does not interact with pancreatic exocrine tissue (15, 16), we thought that the high degree of structural homology with exendin-4 warranted another look at the actions of this peptide.

PACAP-38, a peptide isolated from ovine brain in 1989 (17), interacts with receptors on bovine brain (18) and liver (19) membranes, human neuroblastoma cell membranes (20), and rat pancreatic acinar cell (21), pituitary (22), astrocyte (23), and liver (24) membranes. In dispersed acini from rat pancreas, the biological actions of PACAP-38 appear to be mediated by interaction with VIP receptors (25).

The results presented here indicate that GLP-1(7-36)NH₂, but not PACAP-38, interacts with exendin receptors on pancreatic acini, thereby increasing acinar cAMP. Moreover, the exendin-receptor antagonist, exendin(9-39)NH₂, which blocks the actions of GLP(7-36)NH₂ may be useful as a probe for biological actions of this mammalian exendin analogue.

**MATERIALS AND METHODS**

Male Hartley guinea pigs (150-200 g) were obtained from CAMM Research Lab Animals, Wayne, NJ. HEPES from Boehringer Mannheim; collagenase (type CLS) from Worthington; bovine albumin (fraction V), soybean trypsin inhibitor, bacitracin, and theophylline from Sigma; fetal bovine serum, basal medium (Eagle’s) amino acids (100 times concentrated) from GIBCO; Phadebas amylase test from Pharmacia LKB Biotechnology Inc.; VIP, secretin, PACAP-38, glucagon, GLP-1(1-37), GLP-2(1-34), GLP-1(7-36)NH₂, cholecystokinin(26-33) (CCK-8) from Peninsula, Belmont, CA; [³¹-succinylcAMP from Du Pont-New England Nuclear; cAMP antisera from Du Pont-New England Nuclear; cAMP antisera from

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‡ To whom correspondence and reprint requests should be addressed: SUNY-Health Science Center, 450 Clarkson Ave., Box 1196, Brooklyn, NY 11203-2098. Tel.: 718-270-1112; Fax: 718-270-3107.

§ The abbreviations used are: VIP, vasoactive intestinal peptide; GLP, glucagon-like peptide; PACAP, pituitary adenylyl cyclase-activating peptide; HEPES, 4(2-hydroxyethyl)-1-piperazine ethanol sulfonic acid; CCK, cholecystokinin.
Biomedical Technologies, Stoughton, MA.

Unless stated otherwise, the standard incubation solution contained 24.5 mM HEPES (pH 7.4), 98 mM NaCl, 6 mM KCl, 2.5 mM NaH₂PO₄, 1 mM MgCl₂, 11.5 mM glucose, 5 mM sodium fumarate, 5 mM sodium pyruvate, 5 mM sodium glutamate, 0.5 mM CaCl₂, 2 mM glutamine, 1% (w/v) albumin, 0.01% (w/v) soybean trypsin inhibitor, 1% (v/v) amino acid mixture, and 1% (v/v) essential vitamin mixture. The standard incubation solution was equilibrated with 100% O₂ and all incubations were performed with 95% O₂ as the gas phase.

Dispersed acini from guinea pig pancreas were prepared using methods described previously (26) and suspended in standard incubation solution containing 5 mM theophylline. Amylase release was measured as described previously (26), and amylase activity was determined by the method of Ceska using the Phadebas test (27).

Amylase release was calculated as the percent of amylase activity in the acini at the beginning of the incubation that was released into the extracellular medium during the incubation.

Cellular CAMP was determined by radioimmunoassay using the procedure described previously (28). The concentration of acini in the incubate was adjusted to maintain CAMP on the linear portion of the standard curve. Results for cyclic nucleotide content were expressed as the value obtained with a particular agent (experimental) divided by the value obtained with acini incubated with no additions (control).

Exendin-4, exendin(9-39)NH₂, and [Y²⁵]exendin-4 were synthesized on solid-phase support (PAL resin) using activated N-(9-fluorenylmethoxycarbonyl) amino acids on a Milligen 9050 peptide synthesizer (Milligen, Burlington, MA). Cleavage and deprotection of the peptides were performed in trifluoroacetic acid containing anisole, thioanisole, and ethanedithiol as scavengers. The crude synthetic peptide mixtures were purified by preparative high pressure liquid chromatography. The dose-response curve for [Y²⁵]exendin-4-induced increases in pancreatic acinar CAMP was the same as that with exendin-4.

GLP-l(7-36)NH₂ and GLP-2(1-34)NH₂ (specific activity ~450 and 200 Ci/mmol, respectively) were prepared by iodination with the chloramine-T method with minor modifications described previously (29). [Y²⁵]GLP-1(7-36)NH₂ binding to dispersed acini was measured using procedures published previously for other radioligands (30). The acinar suspension was incubated with 100 PM [³²P]exendin-4 or 100 PM [³²P]GLP-1(7-36)NH₂ for 30 min at 37°C in standard incubation solution containing 0.1% bacitracin. Bound and free radioligand were separated by alternate centrifugation (10,000 × g for 50 s in a Beckmann Microfuge B) and resuspension of acini iniced incubation solution. Total binding for [³²P]exendin-4 and [³²P]GLP-1(7-36)NH₂ was 4.2 ± 1.0 and 12.1 ± 3.4% of added counts (mean ± S.E. from five separate experiments), respectively. Specific binding was calculated as the difference between the amount of [³²P]exendin-4 or [³²P]GLP-1(7-36)NH₂ bound in the absence (total binding) and presence (nonspecific binding) of 1 μM unlabeled exendin-4 or GLP-1(7-36)NH₂, respectively.

There was no difference between binding of [³²P]exendin-4 in the presence of 1 μM unlabeled [³²P]exendin-4 or 1 μM unlabeled exendin-4. In these experiments, nonspecific binding was 34.7 ± 7.3% for [³²P]exendin-4 and 45.0 ± 4.9% for [³²P]GLP-1(7-36)NH₂ (mean ± S.E. from five separate experiments).

Statistical evaluation was performed using Student's t test on paired values or analysis of variance when appropriate for comparison between matched pairs with one control value (Systat, Systat Inc., Evanston, IL). Differences were considered significant when p values were less than 0.05.


GLP-1(7-36)NH₂ Interacts with Pancreatic Exendin Receptors

![Graph](image-url)

**Fig. 1.** Amino acid sequences for exendin-4, GLP-1(7-36)NH₂, GLP-2(1-34), glucagon, and PACAP-38. Amino acids that are homologous to those in exendin-4 are shown in bold face. * indicates COOH-terminal amidation. * indicates that NH₂-terminal 6 amino acids (HDEFER) and COOH-terminal glycine of GLP-1(1-37) are not shown.

GLP-1(7-36)NH₂, GLP-2(1-34), glucagon, and PACAP-38. The first phase (~13-fold increase in CAMP) was maximal with 1 nM VIP, whereas the second phase (~27-fold increase in CAMP) was maximal with 1 μM VIP. Like VIP, PACAP-38 also caused a biphasic increase in CAMP, but the second phase (PACAP-38 concentrations > 3 nM) was shifted about 1 log to the left compared to VIP. Exendin-4 and GLP-1(7-36)NH₂ caused a small (4-8-fold) monophase increase in CAMP. Secretin, PACAP-38, and VIP were about 0.5-1 log more potent in stimulating a detectable increase in CAMP when exendin-4 or GLP-1(7-36)NH₂ were added, whereas the other peptides, adding as much as 1 μM glucagon, GLP-1(1-37), or GLP-2(1-34) did not alter basal acinar CAMP.

To determine whether the actions of PACAP-38 or GLP-1(7-36)NH₂ were mediated by interaction with exendin receptors, we examined the effects of adding a specific exendin-receptor antagonist, exendin(9-39)NH₂ (3). We showed that this exendin fragment can serve as a tool to probe for peptides that interact with exendin receptors on dispersed pancreatic acini (2, 3). As shown in Table I, whereas adding 1 μM exendin(9-39)NH₂ did not alter the increase in CAMP caused by secretin, VIP, or PACAP-38, the fragment abolished the actions of exendin-4 and GLP-1(7-36)NH₂. These results suggest that the actions of GLP-1(7-36)NH₂ but not PACAP-38, are mediated by interaction with exendin receptors.
GLP-1(7-36)NH₂ Interacts with Pancreatic Exendin Receptors

Next, we determined the actions of the peptides tested above on amylase release from dispersed acini. As shown in Table II, 1 μM PACAP-38, VIP, or secretin caused a 5-8-fold increase in amylase release. In contrast, the same concentration of exendin-4, GLP-1(7-36)NH₂, glucagon, GLP-1(1-37), and GLP-2(1-34) did not alter enzyme release. These results indicate that as with exendin-4 (2) and nanomolar concentrations of exendin-3 (3), the increase in cAMP caused by GLP-1(7-36)NH₂ does not stimulate amylase release from dispersed acini from guinea pig pancreas.

To study further the effects of exendin(9-39)NH₂ on the increase in cAMP caused by GLP-1(7-36)NH₂, we examined the actions of increasing concentrations of the exendin fragment on the dose-response curve for GLP-1(7-36)NH₂-induced increases in cyclic nucleotide content (Fig. 3, left) and on a fixed concentration (1 nM) of exendin-4 or GLP-1(7-36)NH₂ (Fig. 3, right). As shown in Fig. 3 (left), increasing concentrations of exendin(9-39)NH₂ caused a progressive rightward shift in the GLP-1(7-36)NH₂ dose-response curve. Similarly, as shown in Fig. 3 (right), increasing concentrations of the exendin receptor antagonist caused progressive inhibition of the increase in acinar cAMP caused by 1 nM exendin-4 or GLP-1(7-36)NH₂. The concentration of exendin(9-39)NH₂ required to cause half-maximal inhibition of the actions of GLP-1(7-36)NH₂ (30 nM) was 3-fold greater than that required to inhibit the actions of exendin-4 (10 nM). Nevertheless, the increase in cAMP caused by either peptide was fully inhibited by 1 μM exendin(9-39)NH₂.

Although GLP-1(7-36)NH₂ alone did not alter amylase release (Table II), it was possible that, as observed previously with exendin-4 (31), combination of this peptide with other pancreatic secretagogues might result in potentiation of enzyme release. To investigate this possibility, we examined the effects of increasing concentrations of GLP-1(7-36)NH₂, GLP-1(1-37), and GLP-2(1-34), alone and in combination with 0.3 nM CCK-8, on amylase release (Fig. 4, left). GLP-1(7-36)NH₂, GLP-1(1-37), and GLP-2(1-34) alone did not alter basal acinar amylase release. In contrast, the combination of GLP-1(7-36)NH₂ plus CCK-8 resulted in potentiation of amylase release that was detectable with 0.1 and maximal with 1 nM GLP-1(7-36)NH₂. The combination of CCK-8 plus maximal concentrations of GLP-1(7-36)NH₂ resulted in an approximately 40% increase in amylase release. Amylase release with the combination of CCK-8 plus up to 1 μM GLP-1(7-36)NH₂ or GLP-1(1-37) or GLP-2(1-34) was the same as that observed with CCK-8 alone.

Fig. 4 (right) shows the effects of adding 1 nM exendin-4 or GLP-1(7-36)NH₂ to the dose-response curve for CCK-8-induced amylase release. As indicated by the stars, the addition of GLP-1(7-36)NH₂ caused significant potentiation of amylase release with each concentration of CCK-8 tested. When exendin-4 was added, potentiation of amylase release occurred with CCK-8 concentrations greater than 0.3 nM. The concentration of CCK-8 that caused maximal enzyme release, 0.3 nM, was not altered by the addition of GLP-1(7-36)NH₂ or exendin-4. The potentiating interaction between GLP-1(7-36)NH₂ and CCK-8 was inhibited completely by adding 1 μM exendin(9-39)NH₂ (data not shown).

Combination of GLP-1(7-36)NH₂ with maximal concentrations of bombesin, carbachol, or the calcium ionophore A23187 also resulted in potentiation of amylase release (Table III). In contrast, amylase release with the combination of GLP-1(7-36)NH₂ and VIP, an agent that increases pancreatic acinar cAMP levels (32), was the same as that observed with VIP alone (Table III).

Other investigators reported that the combination of CCK plus GLP-1(7-36)NH₂ did not result in potentiation of amylase release from dispersed acini prepared from rat pancreas (15,16). To determine whether the discrepancy between these reports and our observations in pancreatic acini from guinea pig pancreas was caused by species differences, we repeated the same experiment shown in Fig. 4 (left) using dispersed acini prepared from rat pancreas (Fig. 5). In contrast to our observations using guinea pig pancreas, 1 μM GLP-1(1-37) alone caused a small but significant increase in amylase release from rat acini. Stimulation of amylase release was not observed with lower concentrations of GLP-1(1-37) or any concentration of GLP-1(7-36)NH₂ or GLP-2(1-34) alone. However, as with guinea pig pancreas, small, but significant, potentiation of enzyme release was observed when 0.3 nM CCK-8 was added to concentrations of GLP-1(7-36)NH₂ ≥ 1 nM. The combination of 0.3 nM CCK-8 with up to 1 μM GLP-1(1-37) or GLP-2(1-34) did not cause potentiation of amylase release.

Table I

<table>
<thead>
<tr>
<th>Additions</th>
<th>Cellular cAMP (experimental/control)</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>1.0</td>
</tr>
<tr>
<td>Secretin, 10 nM</td>
<td>66.9 ± 2.3</td>
</tr>
<tr>
<td>VIP, 1 nM</td>
<td>10.3 ± 0.8</td>
</tr>
<tr>
<td>VIP, 1 μM</td>
<td>67.4 ± 6.3</td>
</tr>
<tr>
<td>PACAP-38, 10 nM</td>
<td>32.1 ± 4.2</td>
</tr>
<tr>
<td>Exendin-4, 1 nM</td>
<td>5.9 ± 0.2</td>
</tr>
<tr>
<td>GLP-1(7-36)NH₂, 30 nM</td>
<td>3.1 ± 0.4</td>
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</tbody>
</table>

Table II

<table>
<thead>
<tr>
<th>Additions (1 μM)</th>
<th>Amylase release</th>
<th>% total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>2.1 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Secretin</td>
<td>15.6 ± 0.7</td>
<td></td>
</tr>
<tr>
<td>VIP</td>
<td>12.1 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>PACAP-38</td>
<td>11.1 ± 0.5</td>
<td></td>
</tr>
<tr>
<td>GLP-1(1-37)NH₂</td>
<td>2.5 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Exendin-4</td>
<td>2.4 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td>2.3 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>GLP-1(1-37)</td>
<td>2.4 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>GLP-2(1-34)</td>
<td>2.4 ± 0.1</td>
<td></td>
</tr>
</tbody>
</table>
GLP-1(7-36)NH₂ interacts with pancreatic exendin receptors.

**Fig. 3.** Left, effect of increasing concentrations of exendin(9-39)NH₂ on GLP-1(7-36)NH₂-induced increases in pancreatic acinar cAMP. Right, effect of increasing concentrations of exendin(9-39)NH₂ on increase in acinar cAMP caused by 1 nM exendin-4 or GLP-1(7-36)NH₂. Acini were incubated with indicated concentrations of secretagogues for 30 min at 37°C. In each experiment, each value was determined in duplicate and results given are means ± S.E. from four separate experiments.

**Fig. 4.** Left, effect of increasing concentrations of GLP-1(7-36)NH₂, GLP-1(1-37), and GLP-2(1-34), alone and in combination with 0.3 nM CCK-8, on amylase release from dispersed acini from guinea pig pancreas. Right, effect of increasing concentrations of CCK-8, alone and in combination with 1 nM exendin-4 or GLP-1(7-36)NH₂, on amylase release from dispersed acini from guinea pig pancreas. Acini were incubated with indicated concentrations of secretagogues for 10 min at 37°C. In each experiment, values were determined in duplicate, and results are means ± S.E. from seven separate experiments. *, **, and *** indicate values that are significantly greater (p < 0.05, 0.01, and 0.001, respectively) than the values observed with the agonist alone.

**TABLE III**

<table>
<thead>
<tr>
<th>Additions</th>
<th>Amylase release</th>
<th>% total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alone</td>
<td>Plus 1 nM GLP-1(7-36)NH₂</td>
</tr>
<tr>
<td>None</td>
<td>1.2 ± 0.1</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Carbachol, 30 nM</td>
<td>3.8 ± 0.2</td>
<td>5.1 ± 0.2**</td>
</tr>
<tr>
<td>Bombesin, 30 nM</td>
<td>5.6 ± 0.2</td>
<td>6.4 ± 0.2*</td>
</tr>
<tr>
<td>A23187, 100 nM</td>
<td>3.6 ± 0.1</td>
<td>4.9 ± 0.3*</td>
</tr>
<tr>
<td>VIP, 10 nM</td>
<td>3.8 ± 0.1</td>
<td>4.0 ± 0.1</td>
</tr>
</tbody>
</table>

induced amylase release (Fig. 4, left). With either radioligand, half-maximal inhibition of binding occurred with 1-3 nM of exendin-4 or GLP-1(7-36)NH₂. Specific binding of $^{125}$I-[Y9] exendin-4 in the presence of a combination of 1 μM exendin-4 plus 1 μM GLP-1(7-36)NH₂ (−1.2 ± 2.4%, mean ± S.E. from five separate experiments) was not different from that observed with 1 μM exendin-4 alone. Similarly, specific binding of $^{125}$I-GLP-1(7-36)NH₂ in the presence of a combination of 1 μM exendin-4 plus 1 μM GLP-1(7-36)NH₂ (4.8 ± 9.6%, mean ± S.E. from five separate experiments) was not different from that observed with 1 μM GLP-1(7-36)NH₂ alone. Glucagon, secretin, VIP, carbachol, and CCK did not alter the binding of $^{125}$I-[Y9]exendin-4 or $^{125}$I-GLP-1(7-36)NH₂ to dispersed acini from guinea pig pancreas (data not shown).

**DISCUSSION**

Our findings indicate that the mammalian peptide GLP-1(7-36)NH₂ interacts with exendin receptors on dispersed acini from guinea pig pancreas to increase cellular cAMP. Evidence for this conclusion includes the following observations. 1) Like exendin-4, GLP-1(7-36)NH₂ alone causes an increase in acinar cAMP without stimulating amylase release. 2) Like exendin-4, GLP-1(7-36)NH₂-induced increases in cAMP are progressively inhibited by increasing concentrations of the specific exendin-receptor antagonist, exendin(9-39)NH₂. 3) Like exendin-4, addition of GLP-1(7-36)NH₂
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results in potentiation of amylase release caused by CCK and other secretagogues that increase acinar calcium concentration (31, 32). 4) The concentrations of GLP-1(7-36)NH$_2$ that stimulate an increase in cAMP are the same as those that potentiate CCK-induced amylase release. 5) Potentiating interactions of GLP-1(7-36)NH$_2$ on amylase release are blocked by adding exendin(9-39)NH$_2$. 6) Specific binding of $^{125}$I-[Y$_{39}$]exendin-4 to dispersed acini from guinea pig pancreas is inhibited by GLP-1(7-36)NH$_2$. 7) Specific binding of $^{125}$I-GLP-1(7-36)NH$_2$ to dispersed acini from guinea pig pancreas is inhibited by exendin-4.

Regarding these last two observations, different patterns of inhibition of binding were seen depending upon the radioligand used. Whereas exendin-4 was a slightly more potent inhibitor of $^{125}$I-[Y$_{39}$]exendin-4 binding, GLP-1(7-36)NH$_2$ was a more potent inhibitor of $^{125}$I-GLP-1(7-36)NH$_2$ binding. These results suggest that exendin-4 and GLP-1(7-36)NH$_2$ may interact with more than one class of acinar receptors. To address this issue, studies are underway to characterize the number, affinities, and molecular masses of acinar-binding sites for radiolabeled exendin-4 and GLP-1(7-36)NH$_2$.

Currently, we cannot explain why exendin-4 or GLP-1(7-36)NH$_2$-induced increases in acinar cAMP do not result in stimulation of amylase release. This may be an example of compartmentation of the cyclic nucleotide. That is, these peptides may increase cAMP in a cellular compartment that is not accessible to cAMP-dependent protein kinases that mediate enzyme secretion (33). Nonetheless, although this increase in cAMP does not stimulate amylase release alone, our experiments indicate that it can potentiate the actions of agents like CCK, carbachol, and bombesin that increase acinar calcium concentration (32). Other actions, if any, of the increase in cAMP caused by these agents remain to be determined.

It is necessary to comment on the differences between our results and those of other investigators who reported the absence of potentiating interactions between GLP-1(7-36)NH$_2$ and CCK on amylase release from rat pancreatic acini (15, 16). Species differences in the structure of the peptide or the response of dispersed acini cannot explain this discrepancy because the amino acid sequences of rat and guinea pig GLP-1(7-36)NH$_2$ are the same (9) and we demonstrated potentiation of amylase release in dispersed acini from both species. However, we can offer possible solutions to this problem. First, our data suggest that contrary to the results with other peptides (34), potentiating actions between GLP-1(7-36)NH$_2$ and CCK are more pronounced in guinea pig than in rat acini (see Figs. 4 and 5). Hence, the small degree of potentiation observed in rat pancreas might be missed if experimental conditions, such as the incubation time, were different. Second, Fehmann et al. (16) presented data examining the interaction of various concentrations of CCK-8 with only one concentration of GLP-1(7-36)NH$_2$, 10 pm (their Fig. 2). In dispersed acini from guinea pig or rat pancreas, we also could not demonstrate a potentiating interaction between CCK and 10 PM GLP-1(7-36)NH$_2$ (Figs. 4 and 5). Potentiating interactions were observed only with concentrations of GLP-1(7-36)NH$_2$ ≥ 1 nm. Further studies will be needed to elucidate the cellular mechanisms underlying this example of postreceptor modulation of amylase release.

The role of truncated GLP-1, that is, GLP-1(7-36)NH$_2$ as the biologically active form of this peptide was first recognized in a rat pancreatic islet cell line in 1987 (35). Subsequently, this peptide has been reported to potentiate glucose-induced insulin release from pancreatic islets (36); stimulate insulin secretion and suppress glucagon secretion in rats (37, 38), dogs (38), pigs (13) and humans (14); stimulate somatostatin secretion from pig pancreas (39); stimulate cAMP production in rat brain (40); and to inhibit pentagastrin-induced gastric acid secretion in humans (41) but, paradoxically, to stimulate parietal cell function in rats (42). Potentiating interactions between GLP-1(7-36)NH$_2$ and CCK have been observed on
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Physiological role of GLP-1(7–36)NH₂ in any of these processes, including pancreatic enzyme secretion, remains speculative. The observation in the present study that exendin(9–39)NH₂ acts as a potent GLP-1(7–36)NH₂ antagonist indicates that the exendin fragment may be a useful tool for determining the physiological actions of GLP-1(7–36)NH₂.

REFERENCES