Photopharmacology

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Optical Control of Insulin Secretion Using an Incretin Switch

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Abstract: *Incretin mimetics are set to become a mainstay of type 2 diabetes treatment. By acting on the pancreas and brain, they potentiate insulin secretion and induce weight loss to preserve normoglycemia. Despite this, incretin therapy has been associated with off-target effects, including nausea and gastrointestinal disturbance. A novel photoswitchable incretin mimetic based upon the specific glucagon-like peptide-1 receptor (GLP-1R) agonist liraglutide was designed, synthesized, and tested. This peptidic compound, termed* ***LirAzo****, possesses an azobenzene photoresponsive element, affording isomer-biased GLP-1R signaling as a result of differential activation of second messenger pathways in response to light. While the trans isomer primarily engages calcium influx, the cis isomer favors cAMP generation.* ***LirAzo*** *thus allows optical control of insulin secretion and cell survival.*

Type 2 diabetes (T2D) currently affects approximately 8% of the global adult population. This syndrome can be best described as a failure of the pancreatic beta-cell mass to adequately compensate for peripheral insulin resistance by secreting sufficient hormone.[1] The resultant dysregulated glucose and lipid metabolism underlie a range of undesirable sequelae, including heart, vascular, nerve, and renal diseases.[2] In the majority of cases, adequate control over T2D can be achieved through lifelong medication together with diet and exercise. To this end, incretin mimetics, i.e., drugs based upon gut-derived glucose-lowering hormones, have rapidly become first-line antidiabetics for the maintenance of normoglycemia.[3] Indeed, long-acting analogues of the endogenously released incretin glucagon-like peptide-1 (GLP-1) have been shown to: 1) potently augment insulin release in a glucose-dependent manner; 2) induce profound weight loss through actions on the brain; and 3) slow down beta-cell failure through pro-survival/anti-apoptotic effects.[4] While such traits undoubtedly make the incretin class attractive candidates for the management of T2D, adverse effects have already been associated with their use, including an increased risk of pancreatitis (causality unclear),[5] gastrointestinal disturbance, and nausea.[6] Methods for targeting drug activity to the tissue of interest would thus provide a desirable refinement to the treatment of T2D with incretin mimetics. Photopharmacology is well-adapted for these purposes, since it harnesses the spatiotemporal precision of light to finely control biological processes (see Figure S1 in the Supporting Information)[7] and is applicable to the pancreas.[8]

Building on previous studies with photocontrolled chigolin, nNOS derivatives, and fluorescence reporter peptides,[9] we reasoned that optical control over the incretin axis could be afforded by installing photoresponsive elements on liraglutide, a stabilized GLP-1 analogue (Figure 1 a,b).[6,10]

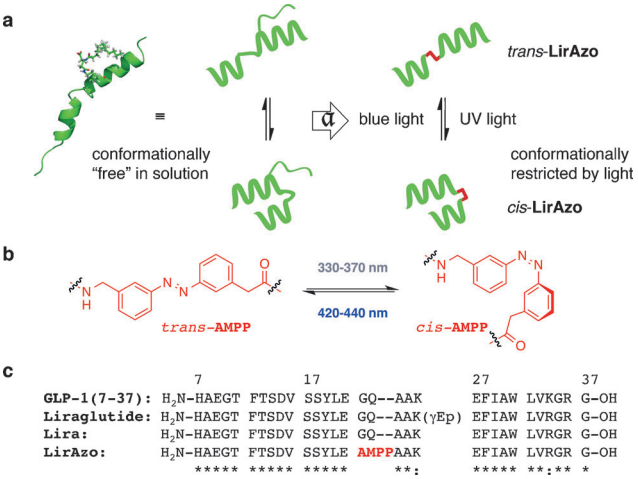


Figure 1. Logic, design, and primary structure of **LirAzo**. a) The liraglutide NMR structure (PDB ID: 4apd) served as a template for the synthesis of **LirAzo**, which differs in the placement of AMPP (red) between the helices (**a** = azologization). b) *cis*-AMPP and *trans*-AMPP are formed upon illumination with UV and blue light, respectively. c) The amino acid sequence of **LirAzo**, showing the replacement of ^{22}G–^{23}Q by AMPP (p = palmitoyl).

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To reliably access glucagon-like peptide-1 receptor (GLP-1R) photoactivation through geometric alterations to ligand structure, an azobenzene photoswitch comprising the amino acid [3-(3-aminomethyl)phenylazo]phenylacetic acid (AMPP)[9b,11] was incorporated into liraglutide. To minimize disruption to helix folding, AMPP was inserted as a bridge between the two α-helices of liraglutide (PDB ID: 4apd; Figure 1a), replacing amino acids ^{22}G-^{23}Q, to obtain **LirAzo** by solid-phase peptide synthesis (Figure 1c and Table S1 in the Supporting Information). NMR spectra were recorded with 35% aqueous [D_3]trifluoroethanol to prevent aggregation, as previously reported (PDB ID: 1d0r),[12] thus providing further evidence for correct folding and in vitro behavior of **LirAzo**.

To compare **LirAzo** with liraglutide, we synthesized a benchmark peptide, termed "Lira", in which the palmitoyl (γEp) moiety at ^{26}K was omitted. This residue, originally introduced to improve plasma binding and half-life in vivo,[6] is unnecessary for in vitro studies.

The *cis–trans* isomerization of **LirAzo** was initially assessed by UV/Vis spectroscopy (Figure 2a). Switching kinetics in response to blue ($\lambda = 440$ nm; *cis*→*trans*) and UV ($\lambda = 330$ nm; *trans*→*cis*) light were robust and fast, with no evidence of degradation or bleaching (Figure 2b; see Figure S2 and Table S2 in the Supporting Information). **LirAzo** displayed remarkable bistability when switched to its *cis* state and subsequently left in the dark (Figure 2c), thus allowing pre-illuminated **LirAzo** to be applied to tissue. GLP-1 binds the GLP-1R through interactions with both the extracellular (^{22}G–^{37}G) and lipid bilayer (7TM domain) portions (Figure S3).[13] From this, it can be predicted that *cis*- and *trans*-**LirAzo** divergently activate receptor signaling by altering one or both of the helical interactions, rather than providing a simple "on–off" switch.

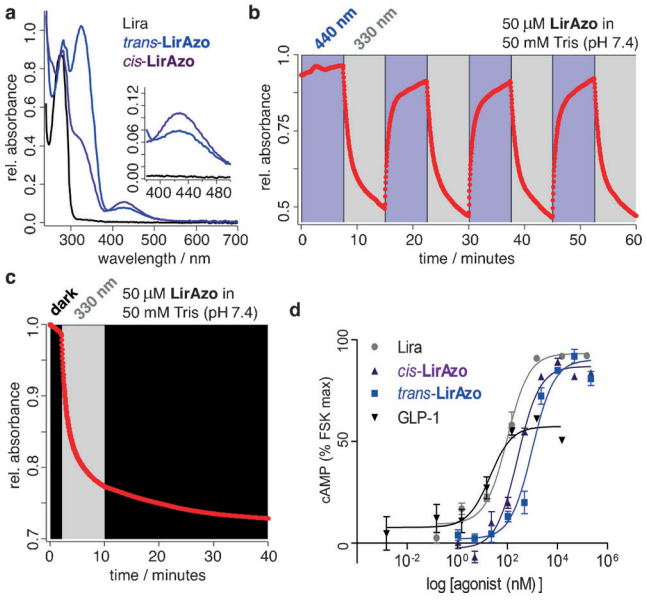


Figure 2. Photoisomerization and potency of **LirAzo**. a) UV/Vis spectra for *cis*-(purple) and *trans*-(blue) **LirAzo**, as well as Lira (black). Inset: n–π* band expanded. b) Reversible and repeated toggling of **LirAzo** between its *cis* and *trans* isomers by using blue ($\lambda = 440$ nm) and UV ($\lambda = 330$ nm) light. c) Bistability of the *cis* state over 30 min. d) cAMP concentration–response studies in CHO-GLP-1R cells, determined by Promega cAMP-Glo assay. Values plotted are the mean ± standard error of the mean (SEM; $n = 3$ repeats).

Accompanying alterations to peptide secondary and tertiary structure were confirmed by CD spectroscopy (Figure S4). While Lira exhibits CD signals typical of α-helix possession, only the *trans* isomer of **LirAzo** shows signals similar to those of Lira. *cis*-**LirAzo**, however, features diverging CD signals (weak maximum at $\lambda = 189$ nm) consistent with the predicted (partial) helix unfolding (Figure S4a). Moreover, in the near-UV region, the signal of *cis*-**LirAzo** rises to a maximum ($\lambda = 326$ nm) that can be assigned to the *cis*-azobenzene moiety in a chiral environment (see Figure S4b).[14] NMR spectra for Lira and **LirAzo** unambiguously demonstrate differences in AMPP and folding behavior upon *cis–trans* isomerization (see the Supporting Information for full NMR spectra and Table S3 for annotation). These findings are of interest, since changes in the secondary and tertiary structure dictate key pharmacological properties, including half-life, permeability, and mode of action. While the former two require complex pharmacokinetic studies, the latter can be examined by using functional in vitro assays. To determine the relative potency and specificity of **LirAzo** versus Lira, concentration–response curves were recorded for cAMP generation in CHO cells expressing the GLP-1R (CHO-GLP-1R).[15] The half maximal effective concentration (EC_{50}) values for *cis*-**LirAzo** ($EC_{50} = 262.0$ nM) and *trans*-**LirAzo** ($EC_{50} = 993.6$ nM) were only slightly higher than for Lira ($EC_{50} = 98.9$ nM) and GLP-1 ($EC_{50} = 20.3$ nM; Figure 2d and Table S4). Together, these data suggest that the presence of AMPP does not significantly disturb ligand binding to GLP-1R.

We next sought to determine the photoswitching properties of **LirAzo** in a more relevant system, namely pancreatic beta cells, in which GLP-1 signals via cAMP and Ca^{2+} to boost insulin secretion.[16] By using intact islets of Langerhans, we confirmed that precise temporal control could be exerted over intracellular Ca^{2+} levels (Figure 3a). Whereas *trans*-**LirAzo** induced increases in the baseline amplitude and frequency of multicellular Ca^{2+} spiking, this was reduced following UV ($\lambda = 350$ nm) illumination to induce *cis*-**LirAzo** accumulation ($P < 0.01$; Figure 3b–f).

Through alternating exposure to blue ($\lambda = 440$ nm) and UV ($\lambda = 350$ nm) light, oscillations in beta-cell activity, which are thought to underlie insulin pulses, could be induced (Figure S5a,b). The effects of *trans*-**LirAzo** on Ca^{2+} levels were abolished by blockade of the GLP-1R with the specific antagonist exendin 9–39 (see Figure S5c,d). Furthermore, *trans*-**LirAzo** was unable to stimulate changes in beta-cell activity in the presence of non-permissive (i.e. low) glucose concentrations (Figure S5e,f), a prerequisite for proper incretin action.[4] In all cases, results in islets were recapitulated in immortalized MIN6 beta cells, which are more amenable to high-throughput assays (see Figure S5g,h). While *cis*-**LirAzo** was able to stimulate Ca^{2+} fluxes, these were only just above those observed following control injection (high glucose alone; see Figure S6).

We next determined the effects of **LirAzo** on cAMP generation, another key pathway through which incretins act

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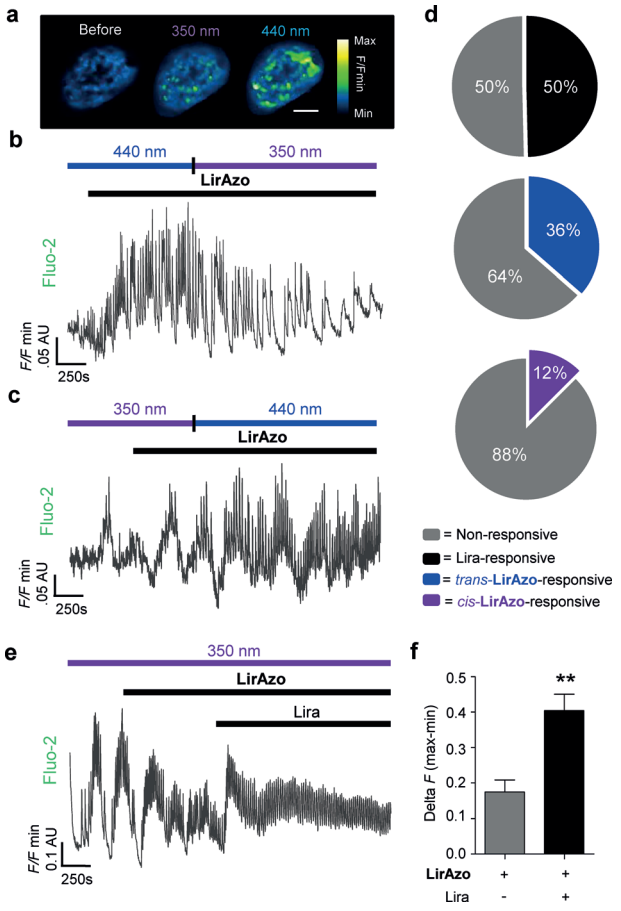


Figure 3. Photoswitching of ionic fluxes in pancreatic beta cells. a–c) Increases in cytosolic Ca^{2+} levels are larger in **LirAzo**-treated islets exposed to blue (*trans*) versus UV (*cis*) light ($n=8$ recordings). d) Pie charts showing the proportion of beta cells within intact islets that respond to Lira, *trans*-**LirAzo** (blue light), and *cis*-**LirAzo** (UV light; $n=8$ islets). e–f) Positive control showing stimulation of cytosolic Ca^{2+} levels following the application of Lira but not *cis*-**LirAzo** ($n=5$ recordings). Lira/**LirAzo** were applied at 150 nM in the presence of permissive (>8 mM) glucose concentration. **P < 0.01 versus **LirAzo**. Values are given as the mean ± SEM.

naled via the cAMP binding partners Epac2 and PKA, as well as IP_3, a second messenger that mediates the release of Ca^{2+} from the endoplasmic reticulum. However, only the former isomer was able to couple properly to ATP-sensitive K^+ channel (K_{ATP}) and voltage-dependent Ca^{2+} channel (VDCC) activity (Figure S8a,b). By contrast, Lira triggered all signaling pathways tested, as expected (Figure S8c). The minor effects of *cis*-**LirAzo** on ionic fluxes are thus mediated through liberation of Ca^{2+} from intracellular stores, whereas *trans*-**LirAzo** stimulates Ca^{2+} influx to support the $Ca^{2+} \gg$ cAMP bias.

Given that **LirAzo** was able to confer light-sensitivity on GLP-1R signaling, we wondered whether it would also allow photocontrol of insulin secretion. To examine this, mouse islets were incubated with **LirAzo** and exposed to either dark or light ($\lambda = 350$ nm). Whereas *cis*-**LirAzo** augmented glucose-stimulated insulin secretion equipotently to Lira (ca. 2.5-fold), *trans*-**LirAzo** was much less effective (ca. 1.4-fold; Figure 5a). This was unlikely to be the result of effects on cell viability, since cytotoxicity was not detected by either dead:live or TUNEL assays following 3 hr exposure of cells to **LirAzo** (see Figure S9). Finally, only the *trans* isomer of **LirAzo** was able to offer significant protection from a 24 h glucolipotoxic insult, which induces beta-cell failure through apoptosis (Figure 5b).

In the present study, we describe a photoswitchable GLP-1R agonist based on liraglutide, which allows unprecedented optical control of a class B GPCR and insulin secretion in pancreatic beta cells. Intriguingly, signal bias could be introduced depending on isomerization status, most likely owing to the pronounced effects of azobenzene orientation on peptide structure. This phenomenon is well-reported for the GLP-1R[15,18] and forms the basis of intense research efforts, since drug side effects may stem from presently unknown signaling interactions.[19] The GLP-1R is coupled to multiple pathways (e.g., cAMP, PKA, Epac2, ERK, and β-arrestin), however, orthosteric ligands can provoke different receptor conformations to engage distinct signals.[15,18] This is best exemplified by responses to oxyntomodulin, which is biased for cAMP over ERK when compared to GLP-1 7–36.[15,18]

to amplify insulin secretion. As expected from modeling studies of GLP-1–GLP-1R binding interactions,[13a,17] *cis*-**LirAzo** displayed different signaling properties to the *trans* isomer. The cAMP concentration response in MIN6 beta cells was significantly left-shifted, with a higher maximal response for *cis*- compared to *trans*-**LirAzo** (Figure 4a,b). Similar results were observed in CHO-GLP-1R cells (Figure S7 and Table S4). Robust signal bias, shown to be a feature of other GLP-1R agonists,[18] was present at all **LirAzo** concentrations over 4 nM (Figure 4c). Indeed *cis*-**LirAzo** favored cAMP generation, while *trans*-**LirAzo** engaged mainly Ca^{2+} signaling. Mechanistically, both *trans*- and *cis*-**LirAzo** sig-

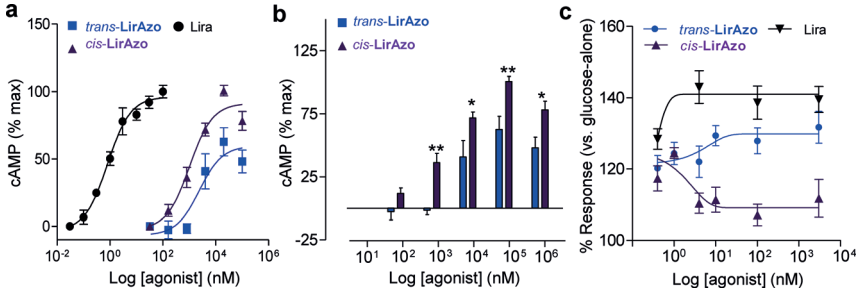


Figure 4. Isomer-biased signaling. a) Photoswitching of cAMP responses in MIN6 beta cells exposed to Lira, *cis*-**LirAzo**, or *trans*-**LirAzo**, as determined by Cisbio HTRF cAMP assay ($n=7$ repeats). b) As for (a), but showing that *cis*-**LirAzo** generates significantly more cAMP than *trans*-**LirAzo** at concentrations greater than 10^2 nM ($n=7$ repeats). c) Isomer-biased Ca^{2+} signaling is present at **LirAzo** concentrations greater than 10^1 nM ($n=8$ repeats; Lira shown as a positive control). Cells were retained in permissive (>8 mM) glucose concentration and Lira or **LirAzo** applied at 150 nM. *P < 0.05, **P < 0.01, and NS (not significant) versus *trans*-**LirAzo**. Values are given as the mean ± SEM.

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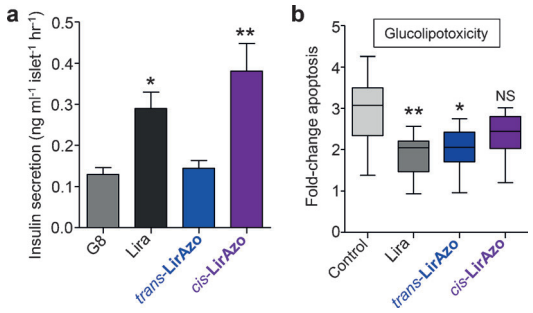


Figure 5. Insulin secretion and apoptosis in pancreatic beta cells. a) Lira and *cis*-**LirAzo**, but not *trans*-**LirAzo**, potentiate glucose-stimulated insulin secretion (G8; 8 mM glucose; $n = 12$ animals). Lira or **LirAzo** were applied at 150 nM in the presence of 8 mM glucose concentration. Values are given as the mean ± SEM. b) Lira and *trans*-**LirAzo** are more protective than *cis*-**LirAzo** against apoptosis induced by glucolipotoxicity ($n = 8$ repeats; the mean and upper/lower quartile are shown with max/min). Lira or **LirAzo** were applied at 500 nM. *$P < 0.05$, **$P < 0.01$ and NS (non-significant) versus G8 or control.

Such divergent effects likely arise from interactions with specific conserved polar residues.[20]

The fine control offered over GLP-1R molecular pathways by **LirAzo** may hence provide a novel method to tease apart the mechanisms underlying signal bias in beta cells, thereby enabling the refinement of incretin mimetics. Indeed, we were able to show here that cAMP is the major driver of incretin-potentiated insulin secretion, whereas anti-apoptotic effects are more pronounced in the presence of both cAMP and Ca^{2+}. This has repercussions for the design of specific GLP-1R agonists, since stimulation of both pathways is likely to be beneficial for T2D treatment. While **LirAzo** potency was less than for native liraglutide, it should be noted that concentration–response studies in CHO and MIN6 cells do not translate well to islets of Langerhans, where the effects of GLP-1 on secretion have been detected in the low picomolar range.[21] Lastly, **LirAzo** demonstrated excellent bistability, which facilitates its use in biological studies by circumventing the need for complex imaging setups/expensive light sources.

In summary, **LirAzo** provides a blueprint for the production of anti-diabetic peptides for which light-triggered alterations to peptide folding—emanating from an azobenzene unit wedged between the helices—alters GPCR activity. We anticipate that this, or future variants, may serve as a useful tool for the functional dissection of GLP-1R signaling in health and disease.

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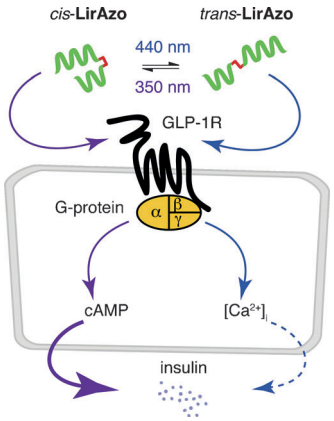
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Communications

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Optical Control of Insulin Secretion Using an Incretin Switch



Incretins in the spotlight: An azobenzene photoswitch was placed between the alpha helices of the incretin mimetic liraglutide to yield isomer-biased optical control over glucagon-like peptide-1 receptor (GLP-1R) signaling, pancreatic beta cell function, and insulin release.

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