DRUG DESIGN

Supramolecularly stabilized diabetes drugs

The stabilization of co-administered insulin and pramlintide with cucurbit[7]uril-conjugated poly(ethylene glycol) in diabetic pigs enhances the overlap of their therapeutic windows.

Kim Henriksen and Morten A. Karsdal

Amylin — a hormone that insulin-producing pancreatic β-cells also secrete[1] — suppresses gastric emptying, reduces prandial glucagon secretion and increases insulin sensitivity[2]. These characteristics are of important therapeutic interest for both type-1 diabetes and type-2 diabetes[2]. However, amylin formulations tend to aggregate in suspension. Pramlintide, a stable, non-fibrillating form of amylin, has led to substantial benefits when administered to patients with diabetes in combination with insulin[2], but the development of pramlintide as a commercial product proved difficult, owing to its unfavourable pharmacokinetics and pharmacodynamics when administered in conjunction with insulin. Currently, the amylin analogue is only approved as an additional therapy to basal–bolus insulin, requiring separate injections with each meal and elevating the risk of postprandial hypoglycaemia unless prandial insulin is carefully adjusted. Hence, pramlintide has not been widely used.

Interest in pramlintide has resurfaced recently, as exemplified by studies reporting promising results from the use of insulin and pramlintide, delivered via infusion pumps, in patients with type-1 diabetes[3]. Yet two separate infusion pumps were required, owing to biophysical and pharmacokinetic incompatibilities between pramlintide and various forms of insulin. An additional complication is that the physiological profiles of insulin and amylin have an insufficient overlap[4,5], a phenomenon thought to result from differences in the hydrodynamic size of multimeric insulin and monomeric pramlintide, which limits their overall efficacy as a co-therapy. Reporting in *Nature Biomedical Engineering*, Eric Appel and colleagues now show that the supramolecular modification of insulin and pramlintide with cucurbit[7]uril-conjugated poly(ethylene glycol) (CB[7]–PEG; CB[7] is a macrocyclic molecule with a high affinity for aromatic amino acids) improves the pharmacokinetic compatibility of the dual-hormone therapy, enhancing post-prandial glucagon suppression when co-administered in diabetic pigs[6]. Because hypersecretion of glucagon during meals is an important complication in patients with either type-1 diabetes or type-2 diabetes, the data suggest a possible route forward for the co-administration of insulin and pramlintide, potentially facilitating the wider applicability of pramlintide and its desirable actions for patients with either disease.

Appel and co-authors non-covalently added CB[7]–PEG to insulin and pramlintide through their aromatic amino acids at the N and C terminus, respectively[7], to generate PEGylated versions of both drugs.

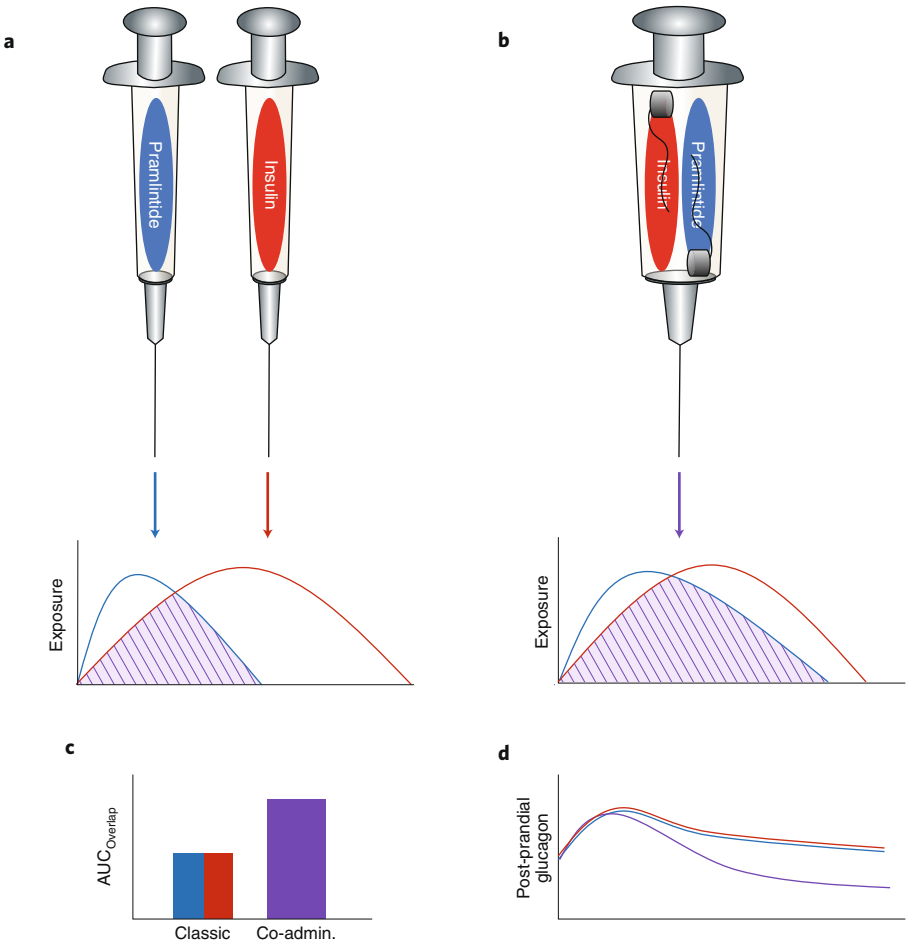

Fig. 1 | The overlap of the functional windows of co-administered insulin and pramlintide is enhanced when the drugs are modified with CB[7]–PEG. a, Exposure curves for the co-administration, with separate syringes, of unmodified pramlintide and insulin. **b**, The co-administration, with one syringe, of CB[7]-PEGylated versions of insulin and pramlintide results in a larger overlap of the drugs' exposure profiles, as indicated by the purple shading. **c**, Areas under the curves (AUCs) for the overlaps in drug exposure. Co-admin., co-administration. **d**, Levels of post-prandial glucagon.

The two CB[7]–PEGylated variants displayed no structural deterioration and no detectable aggregation for 100 hours (unlike the unmodified variants, which aggregate within ten hours in similar conditions). In a rat model of insulin-deficient diabetes and in a diabetic pig model, the authors characterized the pharmacokinetics and pharmacodynamics of the co-formulation, and compared these with the pharmacokinetics and pharmacodynamics of either the unmodified molecule alone or with their successive administration through separate injections in the same animal. In fasting diabetic rats, the co-formulation led to the potent lowering of blood glucose independently of the pramlintide dose (this is expected, as pramlintide primarily works in the prandial state[2]). There were no marked differences in the half-life of insulin when administered alone or as a co-formulation with pramlintide; for the latter, however, the co-formulation led to significantly longer exposure. This indicates that the co-formulation increased the overlap between pramlintide's and insulin's functional windows (Fig. 1), possibly because the hydrodynamic sizes of the CB[7]–PEGylated variants are similar. The overlap in their exposure profiles was also observed in pigs. Notably, although the co-formulation reduced post-prandial glucose levels to the same extent as the administration of both drugs separately, only the co-formulation suppressed post-prandial glucagon secretion. This underscores the co-formulation's potential as a treatment candidate for the correction of insulin and glucagon imbalance in patients with type-1 diabetes, particularly because it should facilitate patient adherence to the dosing regimen.

Appel and colleagues' work suggests that CB[7]-PEGylation (or PEGylation with similar moieties) can improve the delivery and therapeutic efficiency of co-formulations of peptides more generally, provided that the peptides have an aromatic amino acid at the N or C terminus. Translational efforts would benefit from a thorough understanding of the dose-response profile of pramlintide in large animals and then in people with diabetes, and of any toxicity of CB[7]–PEG (on its own and when combined with insulin and pramlintide). In fact, CB[7]–PEG formulations dosed at pharmacologically relevant levels led to elevations in the liver enzymes aspartate transaminase and creatinine in rats and pigs, respectively (the elevations in the pigs were minor, however). Other studies found a benign toxicity profile, at least in mice[8].

Despite pramlintide's ability to induce weight loss and to reduce post-prandial glucose in patients with type-2 diabetes, the drug has limitations in terms of a short half-life and an intrinsically low potency for the activation of the amylin receptor[2]. Peptides with superior agonistic properties to amylin, such as dual amylin-receptor and calcitonin-receptor agonists, activate the receptor for a prolonged period, and may thus reduce the need for multiple daily doses[9]. This class of peptides improves amylin-mediated responses on gastric emptying, glucagon secretion and post-prandial glucose regulation, and regulates weight and induces insulin sensitivity beyond the most efficacious dose of amylin. Their pharmacological potency suggests that the calcitonin receptor can also be a useful target for diabetes drugs[10].

Research into new drugs for type-1 and type-2 diabetes is focusing on combination therapies that explore amylin's mechanism of action. There are preclinical and clinical trials exploring the apparent synergies between amylin-receptor agonists and insulin[3], and between amylin-receptor agonists and insulinotropic molecules (that is, molecules stimulating the production and activity of insulin) such as agonists to the glucagon-like peptide-1 receptor[11]. The objective is to take advantage of amylin's unique ability to increase insulin responsiveness while reducing excessive glucagon levels. Co-formulations of peptide drugs may thus yield favourable outcomes by enabling potent synergies between orthogonal biological pathways. ❐

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Published online: 11 May 2020
https://doi.org/10.1038/s41551-020-0558-1

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Competing interests

K.H. and M.A.K. are employees and stockholders of Nordic Bioscience A/S.