Commentary

MOLECULAR METABOLISM

"Let's Stay Together"; GIP and GLP-1 dual agonism in the treatment of metabolic disease

Richard D. DiMarchi [1]

In this issue of Molecular Metabolism, Coskun and co-authors report the discovery and biological assessment of a novel peptide of sustained duration of action that displays agonism at the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptors [1]. This work presents the characterization of LY3298176 in preclinical studies through early phase clinical evaluation in Type 2 Diabetes Mellitus (T2D). These results represent the foundation upon which the more advanced 26-week clinical study recently reported in Lancet is based [2]. The peptide is structurally derived from the N-terminal fragment of native GIP with alterations that mirror similar changes in previously reported peptides that lead to balanced full agonism at both incretin receptors and pharmacokinetics suitable for once weekly clinical administration. These include an identical substitution at the second position to prevent DPP4 proteolysis and lipidation as observed in semaglutide but with a slightly longer fatty acid [3]. The peptide is C-terminally extended with a Cex-sequence derived from exendin and a mid-sequence non-native amino acid substitution three residues prior to what has been previously reported to result in dual and triple agonism [4–6].

The fatty acylated peptide is a full and highly potent agonist at the human GIP and GLP-1 receptors. The *in vitro* profile is imbalanced in favor of GIP activity ~4–5x based upon relative affinity and activity measurements to native hormones. In human pancreatic beta-cell line (ECN90) the dual agonist demonstrated enhanced efficacy relative to GIP or GLP-1, suggestive of a synergistic virtue in co-agonism. Surprisingly, there is no similar characterization of *in vitro* activity at mouse receptors to support mouse *in vivo* studies. The peptide dramatically improved glucose tolerance in mice at doses of 1 nmol/kg or more and similarly did so at 30 nmol/kg in mice selectively deficient in GLP or GIP receptors, where selective agonists biologically signal only when their respective receptor was present. The dual agonist demonstrated a dose titratable (10, 30, and 100 nmol/kg) reduction in body weight in DIO mice treated for fifteen days, and the lowest dose was nearly twice as effective as semaglutide dosed at three times this level, and seemingly without a proportional decrease in food intake suggestive as previously reported of an additional undefined mechanism of action to support the superior pharmacology [4].

Single dose subcutaneous clinical administration of 0.25–8 mg in healthy volunteers demonstrated a dose proportional increase in plasma concentration (Cmax of ~5–175 nM) with a clearance half-life of nearly five days, supportive of weekly dosing. At a dose of 4.5 mg for four weeks there was a statistically significant reduction in fasting glucose relative to placebo and an improvement in glucose tolerance comparable to a therapeutic dose of dulaglutide at 1.5 mg. Additionally, there was a decrease in body weight of more than four kilograms recorded at this highest single dose, and consistent with a similar reduction in a group dose titrated from 5 to 10 mg dose. Dulaglutide serving as positive control was much less effective in reducing body weight and reflective of prior clinical observations [7]. A similar study of patients with T2D employed single doses of 0.5 or 5 mg each week or two different weekly titration algorithms that increased dose to 10 mg (5/5/10/10) or 15 mg (5/5/10/15). Fasting plasma glucose and insulin were significantly decreased in patients treated with incremental dosing, and the glucose tolerance was improved with each of the three highest dose treatments. Statistically significant body weight reduction in the range of 2–3 kg was observed in the groups administered increasing doses of the dual agonists. Unfortunately, dulaglutide was not comparatively studied in these patients. The safety profile of the drug candidate in this limited duration study largely reflects what is commonly observed for GLP-1 agonists, with GI adverse events being most notable. There was a reversible increase in pulse rate at the two highest doses used in T2D patients, and with dulaglutide treatment of healthy volunteers. It is something worthy of note as dosing is established for more extended treatment in subsequent studies.

These results supplement prior reports that promote dual agonism as an approach to obtain superior efficacy than otherwise possible with GLP-1 agonism alone [4,5,8,9]. The enhanced potency and efficacy to reduce body weight in DIO mice when comparing the extended-acting peptides semaglutide and LY3298176 is consistent with prior results in comparing the shorter-acting peptide liraglutide with the dual action peptide, MAR709 [4]. However, while the current results are suggestive that GIP agonism is the mechanism by which superior performance is achieved, it seems premature to

This commentary refers to ""Let's Stay Together"; GIP and GLP-1 dual agonism in the treatment of metabolic disease by Richard D. DiMarchi", https://doi.org10.1016/j.molmet.2018.09.009.

Department of Chemistry, Indiana University, Bloomington, IN, 47405, United States

[1] RDD is also employed by Novo Nordisk and the views expressed in this commentary are his own.

Received October 5, 2018 • Accepted October 7, 2018 • Available online 12 October 2018

https://doi.org/10.1016/j.molmet.2018.10.004

render a definitive conclusion. The *in vitro* activity of this dual peptide for GLP-1 and GIP receptor potency in mice is not reported and achieving balanced GIP potency across species has proven to be a synthetic challenge. A full, acute dose response in mice deficient for each receptor and similarly chronic treatment of DIO mice would certainly substantiate the conclusion, as relative differences in inherent receptor potency, bioavailability, and PK may contribute to the reported results.

The clinical performance is worthy of note as the peptide has been suitably characterized as a high potency, dual human agonist with an imbalance in favor of GIP agonism. LY3298176 demonstrated time action suitable for once weekly subcutaneous dosing and a linear dose response in the range of 0.25—8 mg. There is a statistically and clinically significant dose proportional increase in metabolic efficacy in volunteers and patients, and notably in the latter when employing a dose titration to 10 and 15 mg. There is no benchmark drug for assessing efficacy in T2D patients, leaving one to compare against reported results for dulaglutide and semaglutide [7]. The peptide appears less potent than either of these two peptides, and, on molar basis, it is worth noting that dulaglutide is ~50x more potent than either peptide [7]. However, the central issues are efficacy and safety. The absence of a specific biomarker to GIP agonism and no positive control in the T2D study elevates the recently reported Lancet study with dulaglutide treatment as the more appropriate measure for addressing this question [2]. In that study, LY3298176 was dramatically more effective in lowering blood glucose and body weight. It adds support to the hypothesis that pharmacologically GIP in concert with GLP can render a difference, much as it does physiologically [8,10].

Regrettably, it is difficult to prove mechanism in humans for drugs with multiple activities as we rarely have subjects selectively deficient in one receptor or access to perfectly matched selective agonists in all measures of pharmaceutical character. Consequently, the preclinical studies translating to human studies with thoroughly assessed reagents constitute an important ingredient to defining the mechanism for superior performance. This report from Coskun et al. [1] should be reviewed in concert with other LY3298176 clinical reports to help define what could constitute an advance in the treatment of T2D, associated with excess body weight [2].

REFERENCES

[1] Coskun, T., Sloop, K., Loghin, C., Alsina-Fernandez, J., Urva, S., Bokvis, K., et al., 2018. LY3298176, a novel dual GIP and GLP-1 receptor dual agonist for the treatment of type 2 diabetes Mellitus: from discovery to clinical proof of concept. Molecular Metabolism 18:3—14. https://doi.org/10.1016/j.molmet.2018.09.009.

[2] Frias, J.P., Nauck, M.A., Van, J., Kutner, M.E., Cui, X., Benson, C., et al., 2018. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet. https://doi.org/10.1016/S0140-6736(18)32260-8.

[3] Lau, J., Bloch, P., Schäffer, L., Pettersson, I., Spetzler, J., Kofoed, J., et al., 2015. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. Journal of Medicinal Chemistry 58(18):7370—7380.

[4] Finan, B., Tao, M., Ottaway, N., Müller, T., Habegger, K., Heppner, K., et al., 2013. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. Science Translational Medicine 5:1—17, 209ra151.

[5] Finan, B., Yang, B., Ottaway, N., Perez-Tilve, D., Smiley, D., Tao, M., et al., 2015. Discovery of a potent, balanced, and integrated triple agonist of glucagon, GLP-1, and GIP that safely reverses obesity. Nature Medicine 21:27—36.

[6] Evers, A., Bossart, M., Pfeiffer-Marek, S., Elvert, R., Schreuder, H., Kurz, M., et al., 2018. Dual glucagon-like peptide 1 (GLP-1)/Glucagon receptor agonists specifically optimized for multidose formulations. Journal of Medicinal Chemistry 61:5580—5593.

[7] Pratley, R.E., Aroda, V.R., Lingvay, I., Lüdemann, J., Andreassen, C., Navarria, A., et al., 2018. On behalf of the SUSTAIN 7 investigators Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Lancet Diabetes Endocrinology 6(4):275—286.

[8] Finan, B., Müller, T., Clemmensen, C., Perez-Tilve, D., DiMarchi, R., Tschöp, M., 2016. Reappraisal of GIP pharmacology for metabolic diseases. Trends in Molecular Medicine 22:359—376.

[9] Frias, J.-P., Bastyr, E.J., Vignati, L., Tschop, M.H., Schmitt, C., Owen, K., et al., 2017. DiMarchi RD the sustained effects of a dual GIP/GLP-1 receptor agonist, NNC0090-2746, in patients with type 2 diabetes. Cell Metabolism 26:343—352.

[10] Campbell, J., Drucker, D., 2013. Pharmacology, physiology, and mechanisms of incretin hormone action. Cell Metabolism 17:1—19.

