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Metabolic diseases such as obesity and type 2 diabetes are increasingly understood as conditions shaped by interconnected pathways spanning glucose regulation, lipid metabolism and energy balance. Addressing this complexity requires coordinated, system-level interventions.

Innovent Biologics is a research-driven biopharmaceutical company exploring innovative medicines for cancer, autoimmune and metabolic disorders. Founded in 2011, the company integrates molecular design, clinical research and large-scale manufacturing, while working to improve patient access to high-quality therapies.

This publication highlights recent advances in metabolic science, focusing on emerging multi-target strategies such as dual agonism. The featured studies explore how coordinating hormonal pathways may enable more comprehensive metabolic management, addressing not only blood glucose but also body weight, lipid metabolism and related risk factors.

Together, these perspectives reflect a field in transition, where biology and therapeutic design converge to address the complexity of metabolic diseases.

人们逐渐认识到，肥胖和2型糖尿病等代谢疾病是由受到血糖调节、脂质代谢和能量平衡的相互关联的信号通路共同塑造的。应对这种复杂性，需要协同的、系统层面的干预措施。

信达生物是一家研发驱动的生物制药公司，致力于开发肿瘤、自身免疫、代谢、眼科等重大疾病领域的创新药物。公司成立于2011年，整合了分子设计、临床研究和大规模生产制造，同时致力于提高患者获得高质量疗法的机会。

本册重点介绍了代谢科学领域的近期进展，聚焦于新兴的双重受体激动剂等多靶点策略。所载研究探索了如何通过协调激素通路，实现更全面的代谢管理，不仅应对血糖，也关注体重、脂质代谢及相关风险因素。

这些观点共同反映出一个正在转变的领域——生物学与疗法设计在此日益交汇，以合力应对代谢疾病的复杂性。

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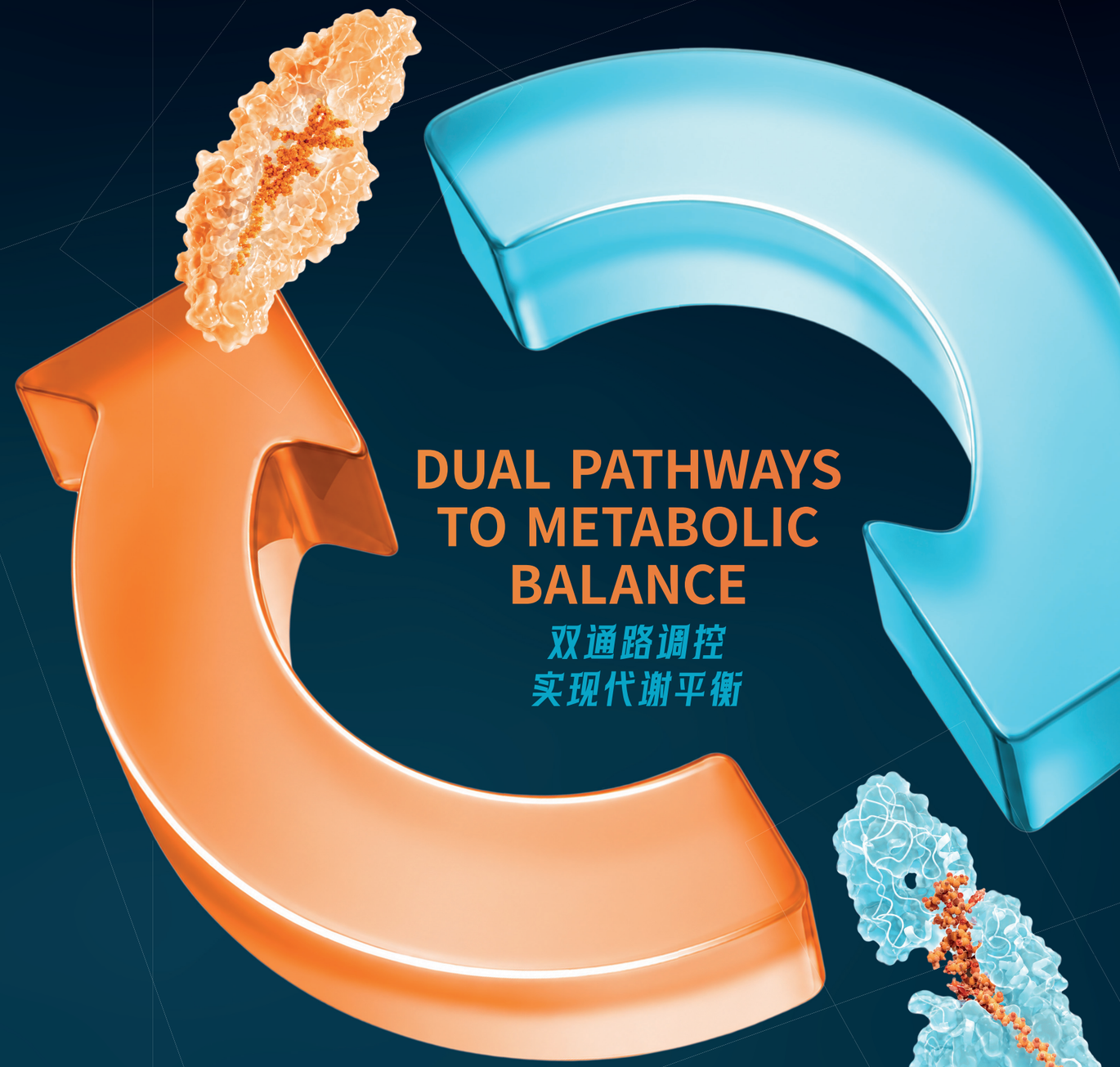
DUAL PATHWAYS TO METABOLIC BALANCE

双通路调控 实现代谢平衡



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A DUAL AGONIST APPROACH TO METABOLIC DISEASE

As metabolic diseases prove challenging for single-pathway therapies, researchers are exploring dual-agonist strategies to coordinate hormonal signals across glucose, lipid and energy expenditure pathways.

Metabolic diseases such as obesity and type 2 diabetes arise from disruptions across tightly coupled physiological processes. For example, the twin-cycle hypothesis proposes that excess lipid accumulation in the liver and pancreas forms reinforcing metabolic loops that contribute to insulin resistance and β-cell dysfunction in type 2 diabetes[1]. Appetite control, pancreatic hormone secretion, hepatic metabolism and whole-body energy expenditure shift together, meaning that altering one single endocrine signal can trigger compensatory responses elsewhere in the system.

Over the past decade, therapeutic development has focused largely on single pathways, most notably glucagon-like peptide-1 (GLP-1), a gut hormone released after meals. GLP-1 receptor agonists link nutrient intake to glucose-dependent insulin secretion and central satiety signalling, improving glycaemic regulation while reducing food intake[2].

However, metabolic dysfunction extends beyond blood glucose regulation. Alterations in lipid handling, hepatic fat accumulation and energy expenditure are also common. During weight loss, reduced energy intake is often countered by adaptive reductions in energy expenditure, therefore limiting long-term efficacy. In type 2 diabetes, improvements in glycaemic control can coexist with abnormal blood lipid levels and fatty liver disease. Current therapies may not address the full spectrum of metabolic dysfunction.

These complexities have driven interest in 'unimolecular polypharmacy', in which a single molecule engages multiple endocrine pathways to address multiple metabolic processes in parallel.

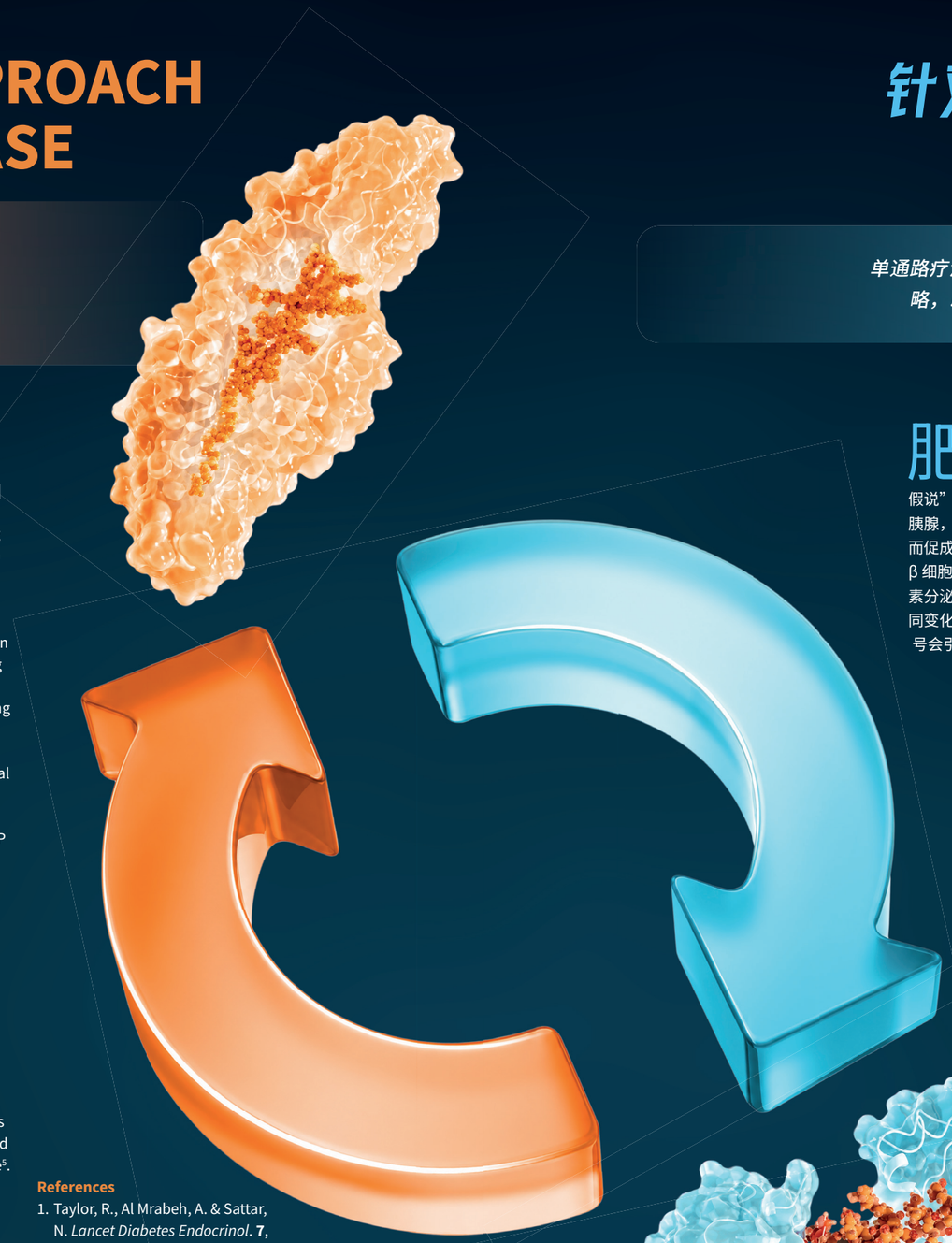
A key player in this strategy is glucagon. Once viewed primarily as a hormone that raises blood glucose by prompting hepatic glycogen breakdown and glucose production, glucagon is now understood to play a broader role in energy and nutrient balance. In the twin-cycle hypothesis, hormones affecting hepatic metabolism can reshape the lipid–glucose feedback loops linking the liver and pancreas.

In the liver glucagon receptor signalling in hepatocytes regulates circulating amino acid turnover by promoting their uptake and conversion to urea. These processes form a feedback relationship between hepatic metabolism and glucagon secretion from pancreatic α cells. Glucagon signaling also facilitates lipid metabolism by increasing fatty-acid oxidation and reducing lipogenesis[3]. Beyond the liver, glucagon receptor activation has been linked to changes in energy expenditure in preclinical models and under low-insulin or fasting conditions in humans[4].

This underpins efforts to co activate GLP 1 and glucagon receptors. The approach hinges on balancing their complementary actions: activation of the glucagon receptor influences hepatic metabolism and energy expenditure, whereas GLP-1 receptor activation supports meal-related insulin secretion and appetite regulation, helping prevent the rises in blood glucose associated with glucagon signalling[2].

Preclinical studies have demonstrated that these activities can be combined within a single molecule, and that the relative balance between the two receptors influences energy balance, body weight and glucose control in diet-induced obese mice[5].

As dual agonist strategies advance, assessment is shifting from glucose-centric endpoints to more integrated metabolic phenotyping, including hepatic lipid handling and energy expenditure. Key questions remain about the relative contribution of each receptor pathway in vivo, the effects of sustained dual signalling and long-term safety in humans. Resolving these uncertainties will be central to judging whether multi-receptor agonism can deliver durable metabolic benefits beyond glucose control alone.



References

1. Taylor, R., Al Mrabeh, A. & Sattar, N. *Lancet Diabetes Endocrinol*. **7**, 726–736 (2019).
2. Baggio, L.L. & Drucker, D.J. *Mol. Metab*. **46**, 101090 (2021).
3. Haedersdal, S. *et al. Nat. Rev. Endocrinol*. **19**, 321–335 (2023).
4. Capozzi, M.E., D'Alessio, D.A. & Campbell, J.E. *Cell Metab*. **34**, 1654–1674 (2022).
5. Day, J.W. *et al. Nat. Chem. Biol*. **5**, 749–757 (2009).

针对代谢疾病的双受体激动剂治疗策略

单通路疗法对代谢疾病作用有限，研究者正在探索双重激动剂策略，以协调葡萄糖、脂质调控和能量消耗等多重激素信号。

肥胖症、2 型糖尿病等代谢性疾病，源于紧密耦合的生理过程紊乱。例如，“双循环假说”提出，过量脂质积聚在肝脏和胰腺，形成相互强化的代谢回路，进而促成 2 型糖尿病中的胰岛素抵抗和 β 细胞功能障碍[1]。食欲调控、胰腺激素分泌、肝脏代谢和全身能量消耗协同变化，意味着改变单一的内分泌信号会引发整个系统别处的代偿反应。

过去十年间，药物的研发主要集中于单一通路，其中尤为引人注目的是胰高血糖素样肽 -1（GLP-1），一种进食后释放的肠道激素。GLP-1 受体激动剂将营养摄入与依赖葡萄糖的胰岛素分泌和中枢饱腹信号相联系，在减少食物摄入的同时改善血糖调节[2]。

然而，代谢功能障碍不仅限于血糖调节异常。脂质代谢紊乱、肝脏脂肪堆积，以及能量消耗变化也十分常见。在减重期间，能量摄入减少常因能量消耗的适应性下降而被抵消，限制长期成效。在 2 型糖尿病中，血糖异常可能与血脂水平异常和脂肪肝同时存在，突显出目前的疗法可能无法应对代谢功能异常的全部问题。

这些复杂情况使人们开始对“单分子多靶疗法”产生了兴趣，其中，多个靶点参与多条内分泌通路，并行调控多种代谢过程。

这个策略的一个关键角色是胰高血糖素（GCG）。它曾被视作主要是通过促进肝糖原分解和葡萄糖生成起作用的提高血糖的激素，如今人们已经发现它在能量和营养平衡中发挥着更广泛的作用。在双循环假说中，影响肝脏代谢的激素能重塑连接肝脏与胰腺的脂质 - 葡萄糖反馈回路。

在肝脏中，肝脏胰高血糖素受体信号通过促进氨基酸摄取和转化为尿素，调节氨基酸循环周转。这些过程形成了肝脏代谢和胰腺 α 细胞胰高血糖素分泌间的反馈关系。胰高血糖素信号还能通过增加脂肪酸氧化、减少脂肪生成来促进脂质代谢[3]。在肝脏之外，胰高血糖素受体的激活已被证明与临床前模型中和低胰岛素及空腹状态下的人的能量消耗改变有关[4]。

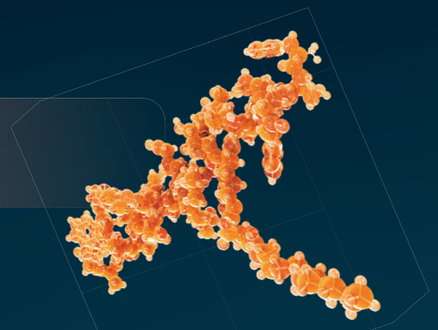
这些结果为协同激活 胰高血糖素样肽 -1 受体（GLP-1R）和胰高血糖素受体（GCGR）提供了基础。这一策略在于平衡两者的互补作用：激活 GCG 受体，影响肝脏代谢和能量消耗，而激活 GLP-1 受体支持与进食有关的胰岛素分泌和食欲调节，有助预防与胰高血糖素信号有关的血糖升高[2]。

临床前研究表明，它们可以被整合于单个分子，两种受体的相对平衡能影响饮食诱导肥胖小鼠的能量平衡、体重和血糖控制[5]。

随着双受体激动剂策略的发展，评估重点正从以血糖为中心转向更综合的代谢表型分析，包括肝脏脂质处理和能量消耗。对于各受体通路在体内的相对贡献，以及人体内持续双重信号的影响和长期安全性，这些关键问题仍待进一步研究。

HOW DUAL-AGONIST APPROACHES COULD CHANGE DIABETES AND OBESITY CARE

As global obesity rates continue to rise, and are a major risk factor for type 2 diabetes, research led by Chinese scientists points to new strategies for obesity and broader metabolic management.



Doctors treating patients with metabolic diseases have often focussed on a single key line on their blood test results: that detailing HbA1c. This is a measure of average blood glucose over the previous few months, and is used as a typical marker of treatment success.

But over time, clinicians aiming to reduce blood sugar spikes began to notice a pattern: some patients showed improved HbA1c numbers, while other parts of the metabolic picture continued to worsen. In some of these patients, liver fat persisted and blood lipids stayed abnormal.

As a major driver of metabolic disease, obesity is recognised as a risk factor for multiple chronic conditions, including type 2 diabetes, fatty liver disease, and cardiovascular disease.

To address the broader metabolic burden associated with obesity, researchers are developing therapies that target multiple hormone receptors. One such candidate is a drug called mazdutide, a 'dual agonist' that activates two separate hormone pathways involved in regulating blood sugar and energy balance.

Across a series of clinical studies led by multiple research centres in China, along with the Innovent Biologics team, mazdutide was found to be associated with reductions in blood glucose and body weight in Chinese adults with type 2 diabetes under trial conditions, alongside changes in metabolic measures such as waist circumference and blood pressure[1,2]. In addition, among study participants who were overweight or obese, mazdutide has also shown the potential to influence longer term metabolic parameters[3].

The authors behind the research argue that a new generation of dual-agonist therapies may enable more comprehensive metabolic management than has so far been possible by addressing a broader spectrum of risk linked to these conditions.

Beyond glucose control

Over the past decade, glucagon-like peptide 1 (GLP-1) receptor agonists have reshaped the treatment landscape for type 2 diabetes. They harness a natural signal from the gut that boosts insulin release after eating to improve glucose control and often lead to at least modest weight loss by reducing appetite and increasing satiety.

Now researchers have begun to explore whether engaging more than one hormonal pathway could build on these effects. As a dual agonist, mazdutide not only targets the GLP-1 pathway, but activates the glucagon receptor, which plays a role in energy metabolism and lipid handling, regulating how the body uses energy and draws on stored fat.

The DREAMS-1 trial began with the most fundamental test. Detailed in a paper in *Nature* in December 2025, this phase 3 randomized study enrolled more than 300 Chinese adults with type 2 diabetes that was not controlled by diet and exercise alone, who were assigned to a once-weekly dose of mazdutide or a placebo. By week 24, the results showed that HbA1c levels had been reduced by about 1.6-2% in the mazdutide group compared with placebo. This was accompanied by average decreases in body weight about 6-8% in that group.

The DREAMS-2 trial, also detailed in a paper in *Nature*, explored the effects of the dual agonist even further. Rather than placebo, the study tested whether its effects differed from a GLP-1–only drug. More than 700 adults with type 2 diabetes were assigned to once-weekly mazdutide or a GLP-1–only drug.

In the mazdutide group, HbA1c level had been reduced by an amount comparable to the GLP-1–only drug, with an additional reduction of about 0.24-0.30% over 28 weeks. Compared to the GLP-1–only drug, participants receiving mazdutide also experienced greater average reductions in body weight, with an additional 4-6% decrease observed under trial conditions.

In both studies, researchers observed changes across a range of other metabolic and organ-related measures, including waist circumference, blood pressure, blood lipids, and other markers linked to metabolic health. The authors argue that this pattern suggests that metabolic changes were coordinated rather than isolated, reinforcing the case for a broader approach to metabolic management.

Rethinking weight control

In China, the number of people who are overweight or obese has risen rapidly over the past four decades. By 2050, the country is projected to have the world's largest overweight or obese population — estimated at more than 600 million people — contributing to a growing burden of chronic diseases[3]. Excess body weight can be accompanied by abnormal blood lipids, elevated blood pressure and early signs of cardiometabolic strain.

Against this backdrop, the researchers behind the studies extended their investigation of mazdutide beyond diabetes. The GLORY programme was designed to test whether the same dual-agonist approach could support a more comprehensive form of metabolic management in adults who were overweight or obese. Detailed in The *New England Journal of Medicine* in May 2025, GLORY-1 was a phase 3 randomized trial conducted in Chinese adults who were overweight or obese, many of whom also had weight-related health conditions[4].

In GLORY-1, more than 600 participants were assigned to once-weekly injections of mazdutide at different doses or placebo and followed for up to 48 weeks. Participants receiving mazdutide on average displayed sustained weight loss over time, compared with minimal change in the placebo group. Average reductions in body weight during the trial exceeded 14%.

Changes were also recorded in waist circumference, blood pressure, blood lipids, and liver health, with many participants seeing liver fat fall by around a third or even by half, alongside reductions in fat mass and self-reported gains in physical function and quality of life. The most common side effects were mild to moderate gastrointestinal symptoms, such as nausea and vomiting.

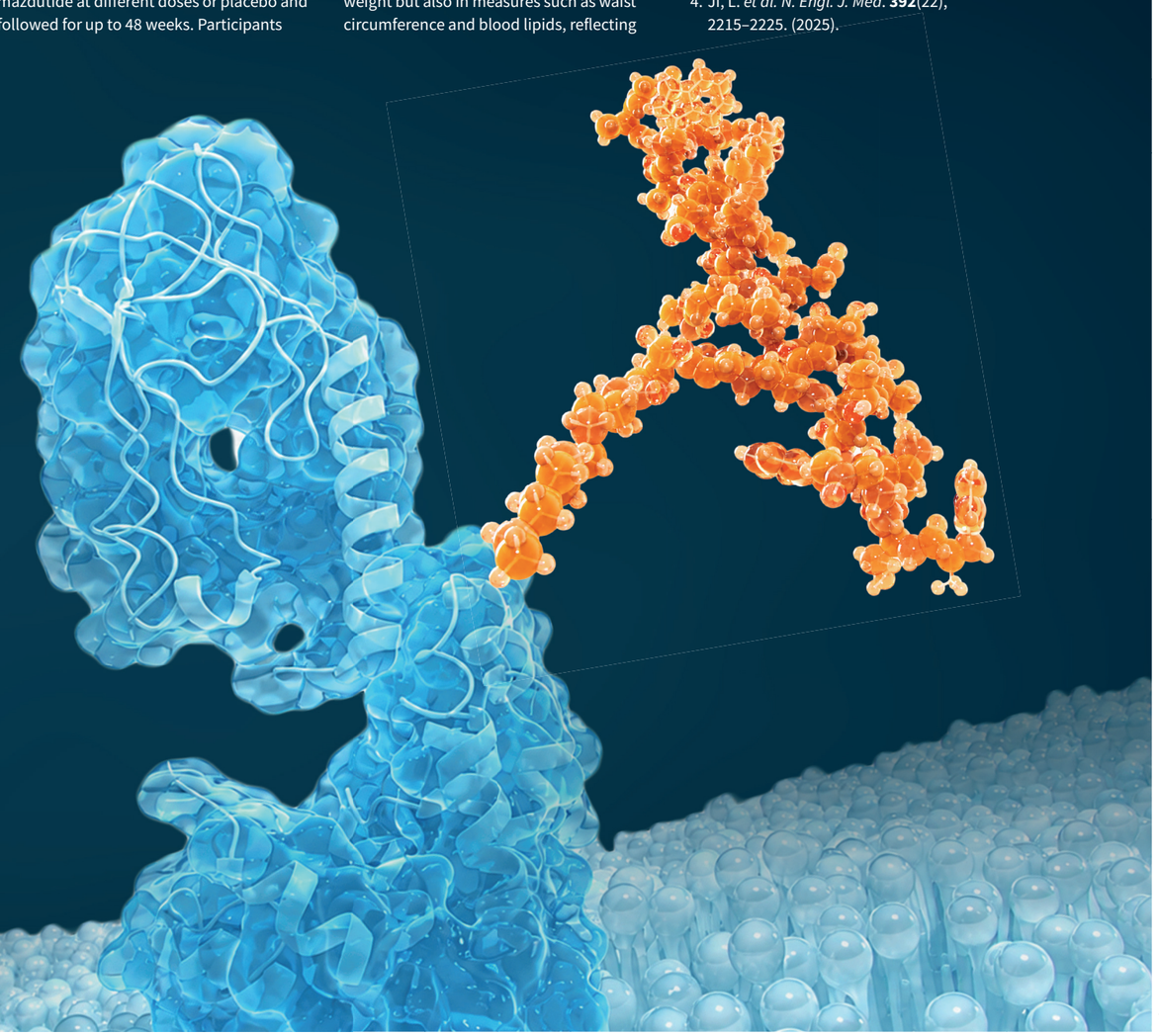
Targeting metabolic systems

Taken together, the DREAMS and GLORY programmes describe a series of studies examining the effects of mazdutide on glycaemic measures, body weight and other metabolic indicators in Chinese adults with type 2 diabetes, who were overweight or obese. Across these studies, investigators reported changes not only in HbA1c and body weight but also in measures such as waist circumference and blood lipids, reflecting the range of endpoints assessed in the trials.

The authors state that significant uncertainties remain. All studies were conducted in a single national population, and follow up durations were restricted to the trial periods. As a result, questions regarding use in broader populations, the durability of effects after treatment discontinuation and the impact on longer term clinical outcomes and will require extended follow up or dedicated outcome studies.

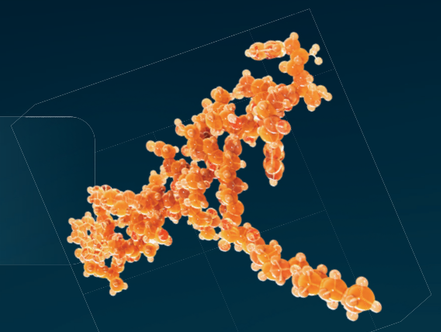
References

1. Zhu, D. *et al. Nature* (2025).
2. Guo, L. *et al. Nature* (2025).
3. Aroda, V. R., & Perreault, L. *N. Engl. J. Med.* **392**(22), 2269-2271. (2025).
4. Ji, L. *et al. N. Engl. J. Med*. **392**(22), 2215–2225. (2025).



双重激动剂策略如何改变糖尿病与肥胖症的治疗

全球肥胖率持续上升；同时，肥胖仍是 2 型糖尿病的主要风险因素。由中国科学家领导的研究为肥胖症和更广泛的代谢管理指明了新策略。



全球肥胖率持续上升；同时，肥胖仍是 2 型糖尿病的主要风险因素。由中国科学家主导的研究为肥胖症和更广泛的代谢管理指明了新策略。

过去在治疗代谢性疾病患者时，医生往往聚焦于血液检测结果中的单项关键指标：糖化血红蛋白（HbA1c）。这一指标用于衡量过去几个月的平均血糖水平，并被用作治疗成功的典型标志。

但随着时间推移，致力于降低血糖波动的临床医生开始注意到一种规律：一些患者的 HbA1c 数值有所改善，但其代谢状况的其他方面却在持续恶化。其中一些患者的肝脏脂肪问题持续存在，血脂也仍然异常。

作为代谢性疾病的重要驱动因素，肥胖被认为是多种慢性疾病的风险因素，包括 2 型糖尿病、脂肪性肝病和心血管疾病。为了解决与肥胖相关的更广泛的代谢负担，研究人员正在开发靶向多个激素受体的疗法。候选药物之一——种名为玛仕度肽（mazdutide）的药物。这是一种“双重激动剂”，可激活两条彼此独立、参与调控血糖与能量平衡的激素通路。

在中国多个研究中心联合信达生物团队开展的一系列临床研究中，在试验条件下，玛仕度肽与中国 2 型糖尿病成年患者血糖和体重的下降相关，同时还伴随腰围和血压等代谢指标的变化 [1, 2]。此外，在超重或肥胖的研究参与者中，玛仕度肽也显示出影响长期代谢指标的潜力 [3]。

研究者们认为，新一代双重激动剂疗法有望通过覆盖与这些疾病相关的更广泛风险谱，实现迄今为止尚未达到的、更全面的代谢管理。

超越血糖控制

在过去十年中，胰高糖素样肽 -1（GLP-1）受体激动剂重塑了 2 型糖尿病的治疗格局。这类药物利用一种来自肠道的天然信号，在进食后增强胰岛素释放，从而改善血糖控制。同时，它们还常常通过降低食欲、增加饱腹感而带来至少一定程度的体重下降。

如今，研究人员已经开始探索结合多个激素通路是否能在这些效果的基础上进一步发挥作用 。作为一种双重激动剂，玛仕度肽不仅靶向 GLP-1 通路，还激活胰高糖素受体。后者在能量代谢和脂质处理过程中发挥作用，调节机体的能量利用方式及脂肪储备的消耗 。DREAMS-1 试验是最基础的验证性研究。该 III 期随机对照临床实验的详细内容发表于 2025 年 12 月的《自然》（Nature）上。试验招募了 300 多名仅靠饮食和运动无法控制病情的中国成人 2 型糖尿病患者，他们被随机分配接受每周一次的玛仕度肽或安慰剂治疗。24 周时结果显示，与安慰剂组相比，玛仕度肽组的 HbA1c 水平降低了约 1.6 至 2.0 个百分点 ，同时该组体重下降约 6-8% 。

同样发表于《自然》的 DREAMS-2 试验则进一步探索了这种双重激动剂的作用。该研究不再以安慰剂为对照，而是比较了双重激动剂与单一 GLP-1 药物的差异。超过 700 名患有 2 型糖尿病的成人被随机分配接受每周一次的玛仕度肽或单一 GLP-1 的药物治疗。在玛仕度肽组中，HbA1c 水平的降幅与仅靶向 GLP-1 的药物相比，在 28 周内额外降低了约 0.24 至 0.30 个百分点。与仅靶向 GLP-1 的药物相比，接受玛仕度肽治疗的参与者的体重下降幅度更大，在试验条件下观察到额外减少了 4-6%。

在这两项研究中，研究人员均观察到了一系列其他代谢和器官相关指标的变化，包括腰围、血压、血脂以及其他与代谢健康相关的标志物。作者们认为，这种规律表明代谢变化是协同的而非孤立的，从而进一步支持了对代谢管理采取更广泛策略的观点。

体重控制的“新思路”

在中国，超重或肥胖的人数在过去四十年中急剧上升 。预计到 2050 年，中国的超重或肥胖人口或将在全球居首，估计超过 6 亿人。这将加剧不断增长的慢性疾病负担 [3]。体重过重可能常伴有血脂异常、血压升高和心血管代谢负荷的早期迹象。

在这一背景下，研究人员将对玛仕度肽的探索延伸到了糖尿病之外。GLORY 项目旨在验证，上述双重激动剂疗法是否能为超重或肥胖的成人提供更全面的代谢管理方案。根据 2025 年 5 月发表于《新英格兰医学杂志》（The New England Journal of Medicine）的一篇研究，GLORY-1 是一项在中国超重或肥胖成人中开展的 III 期随机临床试验，其中许多人同时伴有与体重相关的健康问题 [4]。

在 GLORY-1 中，600 多名参与者被随机分配接受每周一次不同剂量的玛仕度肽或安慰剂注射，并进行了长达 48 周的随访。与安慰剂组微小的变化相比，接受玛仕度肽治疗的参与者随着时间的推移平均表现出持续的体重下降 。试验期间体重的平均降幅超过了 14% 。

研究还记录到腰围、血压、血脂和肝脏健康方面的变化。许多参与者的肝脏脂肪下降了约三分之一，甚至达到一半，同时脂肪量减少，参与者还自我报告了身体功能和生活质量的提高。最常见的副作用是轻至中度的胃肠道症状（如恶心和呕吐）。

靶向代谢系统

综合 DREAMS 和 GLORY 来看，这一系列研究评估了玛仕度肽对中国 2 型糖尿病、超重或肥胖成年人的血糖、体重及其他代谢指标的影响。在这些研究中，研究人员不仅报告了糖化血红蛋白（HbA1c） 和体重方面的变化，还报告了腰围和血脂等指标的变化，这反映了试验中评估的多种终点范围 。

作者指出，研究仍然存在不确定性。所有研究均在单一国家人群中开展，且随访时间仅限于试验期间。因此，关于其在更广泛人群中的应用、停药后疗效的持久性，以及其对更长期临床结局的影响等问题，仍需通过延长随访或专项结局研究来解答。

参考文献

1. Zhu, D. *et al. Nature* (2025).
2. Guo, L. *et al. Nature* (2025).
3. Aroda, V. R., & Perreault, L. *N. Engl. J. Med.* **392**(22), 2269-2271. (2025).
4. Ji, L. *et al. N. Engl. J. Med.* **392**(22), 2215–2225. (2025).