Gut–Brain Hormone Analogues and Metabolic Magic Wand

Worldwide, the prevalence of obesity and adiposity has tripled in the last five decades.[1] The World Health Organization (WHO) reports that one in three adults globally is overweight, and 10% of adults are anthropometrically obese.[2] In the last two decades, a dramatic increase in the prevalence of obesity has been documented from developing countries. The world obesity report suggests that 11% of adults in India are obese.[3] Data from the recent National Family Heath Survey-5 suggests that 44% of males and 41% of females are overweight in India.[4,5]

Understanding the etiopathogenesis of obesity is complex. Monogenic obesity syndromes constitute less than 5% of all cases.[6] In a large majority of individuals with obesity (IWO), the causes are multifactorial and include altered dietary patterns, physical activity and sleep patterns, social circumstances, multiple genetic and epigenetic determinants and environmental determinants. A simple model that uses a quincunx (defined as a quadruple model surrounding a central point) was proposed by Kalra *et al*. about 2 years back. The central point of the quincunx is the energy fulcrum which highlights the imbalance between energy intake and expenditure [Figure 1]. Of the four influencers on this fulcrum, there are two external influences which include as follows: firstly, the physical environment to which the IWO is placed and secondly, the psychosocial environment to which the IWO has been exposed. The other two internal influencers include the hypothalamic – gut axis or the gut–brain axis, involving neural and hormonal signalling between themselves, and lastly the overall functioning of the endocrine system.[7]

Traditionally, obesity guidelines and public health policy have focused on improving the two external influencers.[8-10] The structured lifestyle intervention included planning a healthy meal plan by reducing total energy intake or primarily modifying macronutrient composition to improve adherence. Additionally, an increase in energy expenditure was prescribed which included aerobic physical activity of at least 150 min/week and 2–3 times of resistance exercises per week to preserve muscle mass. Thirdly, IWO were encouraged to reduce sedentary behaviours. Changing the environmental cues of diet and physical inactivity consistently required making changes to the psychosocial environment. Behavioural interventions are summarized succinctly in this review article[11] but require intervention by multidisciplinary teams that include nurses, dieticians, physical activity trainers, clinical psychologists and educators and primarily and add to the large cost of designing any effective public health programme to address obesity. Pharmacotherapy with anti-obesity medications (AOM) in older guidelines was considered as an adjunct to the above lifestyle intervention and was indicated in individuals with BMI ≥30 kg/m^2 or if ≥27 kg/m^2 with additional co-morbidities. IWO with more serious obesity were recommended to undergo bariatric surgery.[8] Overall traditional AOMs prior to glucagon-like peptide-1 receptor analogues (GLP-1RA) led to modest weight reductions of 3–7% after 6–12 months of therapy.

In this issue of the journal, we are focussing on the third influencer of obesity quincunx, the gut–brain axis. Significant success in obesity management has come about in recent years with the use of hormone analogues that target the gut–brain axis. The bidirectional interaction between the brain and the gut plays an important role in appetite regulation, energy expenditure and glucose homeostasis. Within the central nervous system, the hypothalamus and the brainstem are critically involved in sensing metabolic neural and hormonal signals coming from the gastrointestinal tract.[12] The hormones involved in this are summarized in Figure 2.

The review article by Sidrak *et al.*[13] summarizes the currently approved and emerging hormone-based therapies for obesity. The successes of GLP-1As, including Liraglutide and semaglutide, in obesity management far beyond previous AOMs along with a much better safety profile have brought these medications expansive press coverage and breathless influencer and social media updates. Currently, there are

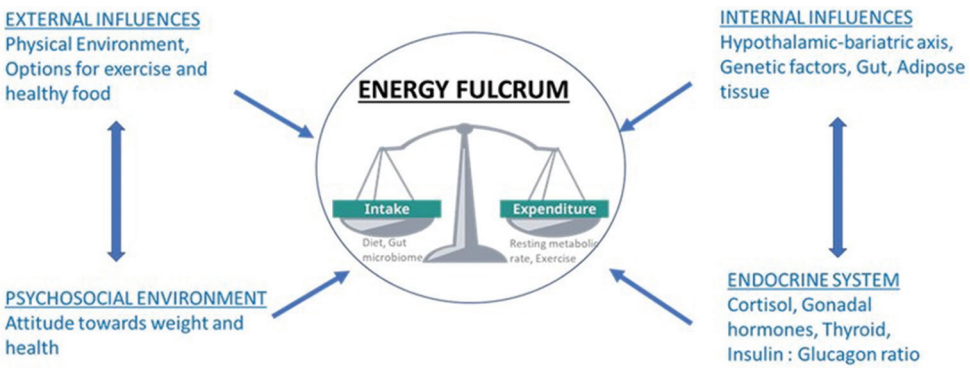

Figure 1: Etiopathogenesis of obesity; the quintessential quincunx

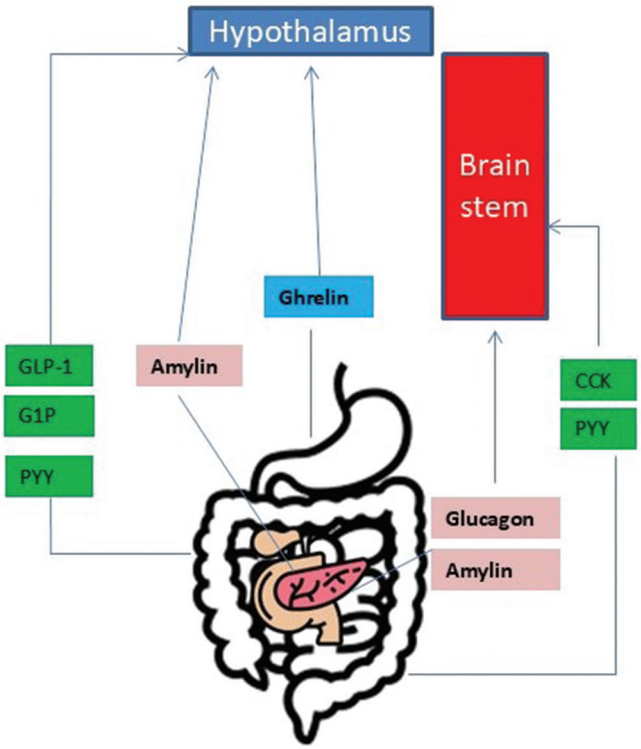

Figure 2: Gut–brain regulation of appetite and energy expenditure. [CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; PYY, peptide tyrosine tyrosine]

three hormone analogues approved for use as AOMs. Wael *et al.* inform us about the huge pipeline of drugs targeting the gut–brain axis. These include more GLP-1RAs, including oral GLP-1RAs, GLP-1RA and GIP (glucose-dependent insulinotropic peptide) dual agonists, long-acting amylin receptor agonists (AMYRA), dual amylin and calcitonin receptor agonists (DACRAs), glucagon receptor (GCGR) agonists, dual GLP-1RA with GCGR dual agonists and triple receptor agonists (GLP-1RA, GIP and GCGR).

This issue also includes a meta-analysis of the efficacy of a combination of semaglutide with a novel AMYRA called cagrilintide. Cagrilintide is a unique long-acting acylated amylin analogue that acts as a non-selective AMYRA. The meta-analysis from three randomized control trials looking at the efficacy of weight loss with this combination (semaglutide 2.4 mg/cagrilintide 2.4 mg dosed once a week) suggests superiority over using semaglutide 2.4 mg/week alone.[14]

Maintaining weight loss is among the most difficult aspects of the management of obesity regardless of the intervention used. In longer-term studies, IWOs who successfully prevent weight regain have to use behavioural therapy strategies which potentially include regular self-weighing, maintaining consistent eating patterns and regular physical activity. However, in a large percentage of patients despite all these interventions, significant weight regain happens.

As endocrinologists used to chronic disease management, we understand the need for lifelong monitoring with treatment escalations and de-escalation for IWO over time. Long-term medication use may become feasible as current hormonal AOMs have now published longer-term cardiovascular safety data suggesting cardiovascular protection in addition to renal protection. Recently, we published an editorial suggesting that we are still looking for a metabolic magic wand in the management of IWO. Long-term use of safe hormonal therapies that work on the gut–brain axis suggests that our metabolic magic wand is close to becoming a reality![15]

Jubbin J. Jacob[1,2]

[1]Department of Endocrinology, Christian Medical College Hospital, Ludhiana, Punjab, India, [2]Department of Endocrinology, Naseem Healthcare, Doha, Qatar

Address for correspondence: Prof. Jubbin J. Jacob, Department of Endocrinology, Christian Medical College Hospital, Ludhiana, Punjab, India.
E-mail: jubbin.jacob@gmail.com

References

1. GBD 2015 Obesity Collaborators; Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, *et al*. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med 2017;377:13-27.
2. World Health Organization. Obesity: Health consequences of being overweight. 2023. Available from: https://www.who.int/news-room/questions-and-answers/item/obesity-health-consequences-of-being-overweight.
3. Lobstein T, Jackson-Leach R, Powis J, Brinsden H, Gray M. World Obesity Atlas 2023. Available from: https://s3-eu-west-1.amazonaws.com/wof-files/World_Obesity_Atlas_2023_Report.pdf.
4. Verma M, Das M, Sharma P, Kapoor N, Kalra S. Epidemiology of overweight and obesity in Indian adults-A secondary data analysis of the National Family Health Surveys. Diabetes Metab Syndr 2021;15:102166.
5. Kalra S, Kapoor N, Verma M, Shaikh S, Das S, Jacob J, *et al*. Defining and diagnosing obesity in India: A call for advocacy and action. J Obes 2023;2023:4178121.
6. Foucan L, Larifla L, Durand E, Rambhojan C, Armand C, Michel CT, *et al*. High prevalence of rare monogenic forms of obesity in obese guadeloupean Afro-Caribbean Children. J Clin Endocrinol Metab 2018;103:539-45.
7. Kalra S, Jacob J, Arora S, Kapoor N. The etiopathogenesis and management of obesity: The quintessential quincunx. J Pak Med Assoc 2023;73:1134-6.
8. Garvey WT, Mechanick JI, Brett EM, Garber AJ, Hurley DL, Jastreboff AM, *et al*. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. Endocr Pract 2016;22 Suppl 3:1-203.
9. S V M, Nitin K, Sambit D, Nishant R, Sanjay K; (on behalf of Endocrine Society of India). ESI clinical practice guidelines for the evaluation and management of obesity in India. Indian J Endocrinol Metab 2022;26:295-318.
10. Chávez-Manzanera EA, Vera-Zertuche JM, Kaufer-Horwitz M, Vázquez-Velázquez V, Flores-Lázaro JR, Mireles-Zavala L, *et al*. Mexican clinical practice guidelines for adult overweight and obesity management. Curr Obes Rep 2024;13:643-66.
11. Jacob JJ, Isaac R. Behavioral therapy for management of obesity. Indian J Endocrinol Metab 2012;16:28-32.
12. Roh E, Choi KM. Hormonal gut-brain signaling for the treatment of obesity. Int J Mol Sci 2023;24:3384.
13. Sidrak WR, Kalra S, Kalhan A. Approved and emerging hormone-based anti-obesity medications: A review article. Indian J Endocr Metab 2024;28:445-60.
14. Dutta D, Nagendra L, Harish BG, Sharma M, Joshi A, Hathur B, *et al*.

Efficacy and safety of cagrilintide alone and in combination with semaglutide (Cagrisema) as antiobesity medications: A systematic review and metaanalysis. Indian J Endocr Metab 2024;28:436-44.
15. Kalra S, Kapoor N, Jacob JJ. Management of obesity: Finding the metabolic magic wand. Indian J Endocrinol Metab 2022;26:499-500.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_460_24

How to cite this article: Jacob JJ. Gut-brain hormone analogues and metabolic magic wand. Indian J Endocr Metab 2024;28:433-5.