Commentary

Reconsidering the Role of Exercise in Incretin Pharmacology: How Physical Activity Might Modulate Incretin Degradation and Drug Efficacy

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Incretin hormones, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are critical regulators of glucose homeostasis and have emerged as foundational agents in contemporary antidiabetic therapy. However, their clinical utility is constrained by rapid enzymatic degradation, primarily via dipeptidyl peptidase-4 (DPP-4). Despite widespread endorsement of exercise as a frontline strategy in managing metabolic disorders, the role of physical activity in modulating incretin pharmacokinetics has been largely overlooked in clinical research. This commentary, inspired by a dismissed inquiry at a pharmaceutical meeting, interrogates the biological plausibility and preliminary evidence linking exercise-induced proteolytic changes to incretin stability. These insights form the rationale for an ongoing scoping review. We argue for the deliberate integration of lifestyle variables into pharmacokinetic frameworks to optimize therapeutic precision and applicability.

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Introduction

Incretin-based therapeutics have transformed the clinical approach to type 2 diabetes mellitus and obesity by leveraging the insulinotropic and glucoregulatory actions of GLP-1 and GIP. Yet, the therapeutic impact of these peptides is attenuated by their rapid breakdown via DPP-4, necessitating the development of enzyme-resistant analogs and inhibitors[1]. Although substantial research has been directed toward optimizing these pharmacological profiles, the potential modulatory role of physiological

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variables—especially exercise—remains insufficiently explored. This commentary highlights an anecdotal yet illustrative dismissal of this concept and proposes its reevaluation through a scientific lens.

A Dinner Table Dismissal: Science Meets Skepticism

During a post-symposium dinner convened by a major pharmaceutical organization, attendees reflected on recent findings from clinical trials evaluating GLP-1 receptor agonists. Amid this discourse, I raised a physiologically grounded query: could exercise influence the degradation kinetics of endogenous or exogenous incretin hormones? The question was met with condescension rather than curiosity, as one senior endocrinologist dismissed the proposition as insignificant.

Pharmacology in Isolation: A Flawed Paradigm

This reaction exemplifies a broader epistemological gap in translational science, wherein pharmacological interventions are often studied in isolation from behavioral and environmental modulators. Physical activity is a universally endorsed, evidence-based intervention for managing metabolic disorders, as reflected in ADA, EASD, and WHO guidelines[2]. However, pharmacokinetic and pharmacodynamic studies frequently neglect to account for exercise either as a confounding factor or a potential modulator. This neglect presupposes physiological neutrality—a premise incompatible with contemporary understanding of molecular metabolism.

Molecular Mechanisms Linking Exercise and Proteolysis

Following this exchange, a focused literature search revealed that physical activity regulates several proteolytic pathways—namely, DPP-4 activity, calpain activation, and the ubiquitin-proteasome system—each of which influences peptide turnover[3][4]. These mechanisms raise a plausible hypothesis: exercise-induced modulation of protease activity could impact incretin degradation, potentially altering drug half-life and efficacy. Although theoretically sound, this intersection remains underrepresented in empirical research.

Toward a Systematic Exploration: The Rationale for a Scoping Review

To systematically evaluate the existing evidence, we are conducting a scoping review that maps the literature on exercise-induced changes in proteolytic systems and their implications for incretin hormone stability. This initiative not only addresses a methodological gap but also aims to challenge entrenched assumptions in drug evaluation paradigms. The outcomes are expected to inform future mechanistic studies and contribute to more nuanced therapeutic guidelines that reflect real-world physiological complexity.

Conclusion

Neglecting exercise as a variable in incretin pharmacology exemplifies an outdated reductionism in biomedical inquiry. In the current era of precision medicine and systems-level approaches, integrating physiological variables such as physical activity is not merely relevant—it is imperative. This commentary calls for a reexamination of conventional research boundaries and advocates for a more holistic view of pharmacological efficacy that accounts for the dynamic nature of human physiology.

Statements and Declarations

Conflicts of Interest

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Declarations

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