Viewpoint

Conquering Metabolic Syndrome: Navigating Pharmacological Avenues for Comprehensive Therapeutics

Metabolic syndrome (MetS) represents a constellation of interrelated metabolic disturbances, including insulin resistance, central obesity, dyslipidemia, and hypertension, which collectively increase the risk of cardiovascular disease and type 2 diabetes mellitus (Alberti et al., 2009). With the global prevalence of MetS on the rise, it has become both a public health and clinical problem (Alberti et al., 2009). Although lifestyle modifications remain a cornerstone of treatment, pharmacological interventions have garnered substantial attention due to their potential to target underlying pathophysiological mechanisms. Hence, this Viewpoint delves into the evolving landscape of pharmacological strategies for mitigating MetS, with an emphasis on the promising role of estrogen receptor-related orphan receptor (ERR) agonists as reported in this issue by Billon et al. (2024). This groundbreaking study explores the potential of an ERR agonist, SLU-PP-332, as an exercise mimetic to address the rising concerns of obesity and metabolic syndrome.

Addressing each component of the MetS is pivotal to curb its impact on global health (Cornier et al., 2008). Traditional therapeutic approaches of pharmacological interventions have demonstrated efficacy in ameliorating various MetS components (Rask Larsen et al., 2018). Insulin sensitizers like metformin and peroxisome proliferator-activated receptor γ (PPARγ) activators (thiazolidinediones) improve insulin sensitivity (Picard and Auwerx, 2002; Bjornstad et al., 2018), contributing to glycemic control and lipid modulation. Lipid-lowering agents such as statins and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have a profound impact on dyslipidemia (Clark, 2003; Pasta et al., 2020). Antihypertensive agents like renin-angiotensin-aldosterone system (RAAS) inhibitors including angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), apart from Ca2+ channel blockers and diuretics, are pivotal in managing hypertension (Unger et al., 2020). The exploration of novel pathways has led to the investigation of emerging pharmacotherapies for MetS. Sodium-glucose cotransporter-2 (SGLT2) inhibitors, initially developed as antidiabetic agents, have demonstrated cardiovascular and renal benefits beyond glycemic control. Their mechanisms of action, including natriuresis and weight loss, hold potential for addressing multiple components of MetS. Additionally, glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide, exenatide), traditionally used for type 2 diabetes, have shown promise in weight reduction and cardiovascular risk reduction (Rask Larsen et al., 2018; Saxena et al., 2023). Emerging evidence highlights the ERRs as promising therapeutic targets in MetS. ERRs are nuclear receptors that play a crucial role in regulating energy homeostasis, mitochondrial biogenesis, and fatty acid oxidation. ERR agonists activate these pathways, addressing key MetS components simultaneously.

Obesity, a significant health concern worldwide, is intricately linked to various metabolic disorders and poses a substantial risk to public health. Several antiobesity drugs have emerged, including orlistat, a lipase inhibitor that reduces fat absorption (Heck et al., 2000), and newer agents targeting appetite-regulating hormones. These agents, although showing promise in weight reduction, often require careful patient selection and monitoring due to potential gastrointestinal and cardiovascular side effects. As physical exercise holds a pivotal role in reducing the risk of metabolic diseases, investigating pharmacological exercise mimetics becomes of paramount importance. The manuscript by Billon et al. (2024) provides a remarkable contribution by presenting compelling evidence for SLU-PP-332 as a promising agent to emulate the metabolic benefits of exercise and ameliorate the metabolic imbalances associated with obesity and metabolic syndrome. This should address several existing controversies whether ERR downregulation or upregulation is beneficial for metabolic disorders (Villena and Kralli, 2008; Casaburi et al., 2018; Tripathi et al., 2020).

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ABBREVIATIONS: ERR, estrogen receptor-related orphan receptor; MetS, metabolic syndrome.
The research commences by elucidating the fundamental roles of ERRs in regulating energy metabolism and fuel preference. Building on these insights, the authors detail the development of SLU-PP-332, a novel ERR agonist of α, β, and γ receptors, with a slight preference for ERR-γ, capable of mimicking the physiological adaptations induced by aerobic exercise without affecting food intake or lean mass. By evaluating the effects of SLU-PP-332 on various metabolic parameters, using the Comprehensive Laboratory Animal Monitoring System, the study demonstrates its potential to enhance fatty acid oxidation, increase energy expenditure, and ultimately reduce fat mass accumulation in mouse models of obesity and metabolic syndrome.

The manuscript effectively bridges the gap between molecular insights and translational applications. The in-depth analysis of metabolic parameters, gene expression patterns, and physiologic responses provides a comprehensive understanding of SLU-PP-332's impact. Additionally, the study addresses potential challenges and offers insights into the balance between therapeutic benefits and potential side effects, highlighting a balanced and cautious approach to its implementation. Notably, Billon et al. (2024) speculate that the agonism of SLU-PP-332 at both α- and γ- ERR receptors could underlie its apparent beneficial effects. Future work should determine the optimum blend of receptor pharmacology for the desired therapeutic benefits.

These findings hold significant promise for future therapeutic strategies in the treatment of obesity and metabolic syndrome. The ability of SLU-PP-332 to simulate exercise-induced benefits without the need for physical activity introduces an innovative avenue for tackling metabolic disorders. Moreover, the manuscript emphasizes the importance of ERRs as targets for pharmacological intervention, revealing the intricate regulatory networks that govern energy metabolism and adaptation. Further studies can elaborate on how ERR activity in tissues beyond skeletal muscle may contribute to the observed effects that would enhance overall understanding of the therapeutic potential. It would be intriguing to gain further insight into recently reported novel ERR agonists and whether they exhibit exercise-mimicking properties (Shinozuka et al., 2021). Also, physical exercise stimulates a variety of cells, tissues, and organs, conferring multiple prohealth advantages, especially psychologic effects pertaining to mood and autonomy (Hawley et al., 2021). Whether SLU-PP-332 could achieve these mood and autonomy health benefits as well remains to be observed. Another important area is the influence of gender as this study relied mainly on male mice. Similar experiments in female mice, preferably ovariectomized to avoid estrus cycle-induced fluctuations, could provide valuable additional information. ERR agonists hold promise not only as standalone agents but also as adjuncts to traditional therapies. Their mechanisms of action can complement those of existing drugs, potentially offering synergistic effects. The combination of ERR agonists with insulin sensitizers, lipid-lowering agents, or GLP-1 agonists that primarily suppress appetite might yield additive benefits in managing multiple MetS components, which could allow for reduced doses of each and accordingly lessened side effects.

In conclusion, the manuscript by Billon et al. (2024) presents an exciting and transformative contribution to the field of pharmacology. The exploration of SLU-PP-332 as an exercise mimic, along with its potential implications for obesity and metabolic syndrome treatment, highlights its significance as a potential therapeutic tool. It is exhilarating to envision the far-reaching implications of this study and its capacity to revolutionize our comprehension of metabolic disorders and therapeutic approaches. Although ERR agonists show immense potential, challenges lie ahead. Ensuring specificity and minimizing off-target effects remain critical. Long-term safety and efficacy data are essential, especially considering the complex interplay of metabolic pathways involved. The rising prevalence of MetS necessitates a comprehensive approach to its management. Throughout history, the treatment landscape for MetS has evolved from lifestyle modifications to a multifaceted approach integrating pharmacological agents targeting key metabolic pathways. This journey underscores the dynamic nature of medical research, the evolving understanding of MetS pathophysiology, and the continuous pursuit of more effective and tailored interventions. Pharmacological approaches, when used judiciously and in conjunction with lifestyle modifications, offer valuable tools in alleviating the various components of MetS. Continued research, informed by an understanding of the intricate interplay of metabolic pathways, holds the promise of refining therapeutic strategies and improving patient outcomes in the battle against this burgeoning global health concern.

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References
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