Editorial

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Hormone based therapy and crosstalk beyond hormones

https://doi.org/10.1515/mr-2024-0052

The growing prevalence of non-infectious diseases is now within the major global public health concerns. Among them, metabolic disorders, including obesity, type 2 diabetes (T2D), hypertension, cardiovascular diseases (CVD), metabolic dysfunction-associated steatotic liver disease [MASLD, previously known as non-alcoholic fatty liver disease (NAFLD)], have been drawing our attention the most. Such prevalence is mainly attributed to the consumption of the Western diet or "fast food", and the sedentary lifestyles. Fortunately, during the past few decades, biomedical researchers from different disciplines have made fundamental advancements of our knowledge on the pathophysiology of those diseases, facilitating the early diagnosis and bringing us novel and potential future novel strategies in the treatment and the prevention of those metabolic disorders.

We have commented recently that during the past half century, dozens of new hormones have been identified, which are not produced by the classical endocrine organs [1]. A few of them are directly involved in metabolic homeostasis, including glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), leptin, ghrelin, fibroblast growth factor 21 (FGF21), and many others [1]. Both GIP and GLP-1 were initially recognized as incretin hormones, as they are able to facilitate postprandial insulin secretion in glucose concentration dependent manner. GLP-1 or incretin based therapeutic agents, including exenatide, liraglutide and semaglutide, are now broadly utilized in the treatment of T2D as well as its various complications [2, 3]. Some incretin based therapeutic agents have also been approved for body weight management in United States of America, Canada, European countries, and elsewhere. During the past decade or more, intensive clinical trials have been conducted in the determination of the therapeutic potential of various FGF21 analogues [4–6]. Furthermore, research on hormone-based therapy for MASLD is entering a new era. We are happy to see that Resmetirom, a thyroid hormone receptor beta (NR1A2) agonist, is now an FDA-approved drug for the treatment of non-cirrhotic and metabolic dysfunction associated steatohepatitis (MASH), as reviewed by Chui et al. for our journal [7]. During the past decades, researchers have also demonstrated the complicated metabolic function of bile acids. The function of bile acids resembles those of hormones, acting via specific receptors including the farnesoid X receptor (FXR), the G protein coupled bile acid receptor, TGR5 and sphingosine-1 phosphate receptor 2 (S1PR2), and others [8, 9]. Gut microbiome is actively involved in bile acid metabolism and homeostasis, and the interaction between bile acids and gut microbiome contributes to the development and progression of metabolic disorders, including health decline and aging [10]. For decades, we have been aware of the connection between sexual hormones and various diseases, especially those with the metabolic impact [11]. Indeed, the function of those sexual hormones is far beyond the reproduction, reviewed by Xega and Liu for our Journal [12].

This year, we have recruited six bench work scientists (along with their team members or colleagues) from the United States of America, Canada, and Hong Kong, China, to present their expert views on six different but related topics in biomedical research on functional study of metabolic hormones or hormonal factors and drugs derived from those hormones [7, 9, 10, 12–14]. Below, I will provide my brief introduction to each of these six review articles.

GLP-1, beyond glucose homeostasis

GLP-1, encoded by the proglucagon gene (*GCG*/*Gcg*) and produced by gut endocrine L cells, was initially recognized as an incretin in stimulating postprandial insulin secretion

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in glucose concentration dependent manner, regulating blood glucose homeostasis [3]. Adeli's team is among the pilots on exploring the function of GLP-1 and its based drugs in lipid homeostasis [15]. The team has made important contribution in demonstrating that GLP-1 or its based diabetes drugs can signal centrally as well as peripherally to reduce both fasting and postprandial lipoprotein secretion. Recently, utilizing the golden hamster as the animal model, Adeli's team showed the existence of a novel vagal neuroendocrine signaling pathway through which GLP-1 may exert its anti-lipemic effect [16]. Here Hoffman and Adeli provided a systematic review on the discovery of GLP-1 and its receptor, as well as the biological function of GLP-1 [13]. Importantly, Hoffman and Adeli have commended the importance of the gut-brain axis in governing intestinal and hepatic lipid metabolism and summarized neural control of hepatic lipoptorin metabolism by GLP-1 during the past decades [13]. In the concluding remarks, Hoffman and Adeli expanded the scope into other gut hormones, including GIP, cholecystokinin (CCK), and peptide YY (PYY), raising the question how GLP-1 works with other gut hormones in modulating intestinal and hepatic lipoprotein production, clearance, and homeostasis via the complex gut-brain-liver axis [13].

Eight years ago, Jin's team contributed a historical review on the hepatic function of GLP-1 [17]. The existence of insulin function independent, or gut-pancreas-liver axis independent, hepatic function of GLP-1 and its based diabetes drugs, explains why those drugs are effective in treating patients with serious insulin resistance, as well as their profound effect on lipid homeostasis. During the past two decades, one of the controversies in the field is whether liver expresses a functional GLP-1 receptor (GLP-1R). Along with the technology advancement, including RNA-seq and single cell RNA-seq (scRNA-seq), we are now clear that either human or mouse hepatocytes do not express the "classical" GLP-1R [18], which was initially isolated by Thorens in 1992 [19]. Liu and colleagues in Jin's team further proved the lack of GLP-1R expression in the mouse liver and demonstrated that the *in vivo* stimulatory effect of peripheral liraglutide treatment on hepatic FGF21 expression cannot be "re-produced" in the *in vitro* settings in mouse primary hepatocytes [18]. They then demonstrated that peripheral liraglutide treatment could not stimulate hepatic FGF21 production or plasma FGF21 hormone level in GLP-1R knockout mice while most metabolic beneficial effects of liraglutide treatment in high fat diet (HFD) challenged mice were either lost or significantly attenuated in liver specific FGF21 knockout mice [18]. Thus, liraglutide (and likely other GLP-1R agonists, GLP-1RAs) may exert its stimulatory effect on hepatic FGF21 via GLP-1R expressed in an extra-hepatic organ and FGF21 is among the essential effectors of GLP-1RAs in executing their metabolic beneficial function [18]. In the current review article for our journal, Feng and Jin further updated the literature review on the hepatic function of GLP-1 and its based diabetes drugs, and commented on the importance of the crosstalk among organs via the gut-liver axis, or the gut-brain-liver axis, or axes that link other peripheral tissues and the brain [14]. In this review article, Feng and Jin have also commented on a recent study by Le and colleagues, showing that peripheral liraglutide treatment induced body weight loss was impaired in liver specific FGF21 knockout mice with high carbohydrate diet challenge or high fat high sugar diet challenge [20]. Notably, neuronal *Klb* (which encodes Klotho beta, the obligatory co-receptor for FGF21) is implicated in mediating the effect of peripheral liraglutide treatment on reducing body weight gain in mice with obesogenic diet challenge [20].

Rezdiffra, the first hormone-based drug for MASLD

As reviewed by Xu and colleagues, multicentre phase-2 clinical trials have been conducted in patients with MASLD or MASH, testing the therapeutic function of semaglutide or other GLP-1RAs [7]. Dozens of clinical trials have also been conducted in testing the beneficial effect of various FGF21 analogues during the past decade [4–7, 21]. In the current review article for our Journal, Xu and colleagues have also reviewed the history of the development of thyroid hormone receptor-beta agonists as therapeutic agents for MASLD or MASH [7]. Among them, resmetirom (MGL3196), sold now under the brand name Rezdiffra, was shown to be effective for resolving noncirrhotic nonalcoholic steatohepatitis and attenuating liver fibrosis [22]. In March, 2024, Rezdiffra was approved by the United States of America Food and Drug Administration (FDA) for its clinical use. In the concluding remarks, Xu and colleagues made their perspective comment: "It is unlikely that a single drug is sufficient to treat all aspects of the disease". As each category of them exhibit "varying degrees of therapeutic benefits for different pathological features", "their combination therapies targeting different aspects of MASLD may produce synergistic and complementary therapeutic benefits". Indeed, fusion proteins of GLP-1RAs and FGF21 have been tested in recent pre-clinical studies, as we have commented [4] while the dual agonist known as tirzepatide that targets both GIP receptor (GIPR) and GLP-1R is now

an FDA proved diabetes drug [23]. In the near future, we anticipate seeing more and more combinational therapeutic strategies that target a given disorder from different pathological features.

Bile acids are emerged as "hormonal factors" from liver to gut and elsewhere

Bile acids are steroid acids, synthesized from cholesterol in hepatocytes, conjugated with taurine or glycine residues to form bile salts. Although primary bile acids are produced in the liver, secondary and tertiary bile acids are formed in the intestine, with the participation of enzymes that are produced by gut microbiome. It has been suggested that bile acids mimic the feature of metabolic hormones that bind to nuclear receptors including FXR and TGR5. Through such mechanism, bile acids mimic the function of hormones in regulating the expression of proteins that are involved in cholesterol homeostasis. In the current review article for our Journal, Zhou and colleagues summarized our current knowledge on bile acid homeostasis, involving their biosynthesis and enterohepatic circulation. They then provided a detailed discussion on mechanisms underlying bile acid homeostasis, involving the feedback inhibition, hormonal control of bile acid synthesis and their interaction with gut microbiota. In addition to commenting FXR and TGR5 as common bile acid receptors, Zhou and colleagues have also made thoroughly review on another G-protein coupled receptor sphigosine-1 phosphate receptor 2 (S1PR2). Zhou's team has made important contributions on function of S1PR2 [24, 25]. S1PR2 can be activated by conjugated primary bile acids including taurocholic acid (TCA) and glycocholic acid (GCA) but not by unconjugated bile acids. Zhou and colleagues commented that "the diverse tissue distribution of S1PR2 underlines its multifaceted physiological and pathological roles". We anticipate seeing further exploration on function of S1PR2 in various organs and mechanisms underlying the pluripotent function of S1PR2 by Zhou's team and by others in the near future, expanding our general knowledge on function of bile acids.

The role of bile acids in human aging was reviewed by Huang and two of his team members for our Journal [10]. As stated by Huang and colleagues in the abstract, "bile acids serve as important signaling molecules that enable fine-turned inter-communications from the liver, though the intestine, to virtually any organ". We learned the reciprocal regulation between bile acids and gut microbiota in this perspective review. Briefly, primary bile acids are synthesized in the liver, secreted into the intestine, where they undergo the transformation into secondary or tertiary bile acids, with various enzymes that are produced by gut microbiota. In turn, bile acids influence the composition of the gut microbiota as they possess the anti-microbial activity and can activate signaling molecules crucial for the maintenance of gut homeostasis. Through a citation from this review, we learned that aging is associated with the decline in bile acid levels and the alteration in bile acid profiles [26]. Mechanistically, the alteration of the dynamic equilibrium between bile acids and gut microbiota may cause intestinal barrier dysfunction, leading to endotoxemia, systemic inflammation, insulin resistance, various metabolic disorders, and overall health decline. The authors have also presented their perspectives on targeting bile acid receptors including FXR, TGR5, vitamin D receptor (VDR) and S1PR2, or targeting gut microbiota, or targeting bile acid synthesis and modification enzymes, to improve intestinal barrier functions, leading to improved health-span and life-span [10]. It is worth mentioning that Huang's team has made important bench work contributions to interactions between gut microbiota and bile acids, including a recent publication on functional exploration of the diabetes drug metformin [27].

Sex hormones exert their functions beyond reproduction

Our mechanistic understanding of function of sexual hormones has advanced tremendously during the past 2–3 decades. In addition to nuclear receptors, these steroid hormones, including estrogens, progesterone and androgens, were also shown to exert their pluripotent functions via membrane bound receptors. Some of the membrane bound steroid hormone receptors belong to the GPCR superfamily. Unlike nuclear receptors, which mediate their effects slowly via genomic mechanisms, membrane bound GPCRs are cell surface receptors that rapidly alter intracellular signaling cascades. Various synthetic agonists and antagonists for those membrane bound receptors are now available for their functional analyses in cultivated cells or animal models. For our journal, Liu and his team member Xega provided an updated overview on the above three sexual hormones [12]. They then thoroughly reviewed the literature on each of them on fat mass, lipid metabolism, and glucose homeostasis. A focus of their review is the role of sexual hormones in CVD, including hypertension, vascular aging, and coronary artery disease. They also reviewed the literature on the role of sex hormone-binding globulin (SHBG) in metabolic syndrome and CVD. In the summary

and perspective, the authors stated that the insights into the roles of these sex hormones could lead to the identification of novel diagnostic and prognostic markers, such as SHBG levels. The cross-disciplinary study by endocrinologists, cardiologists and bench workers may lead to the development of new pharmaceutical treatments that modulate hormone levels or their activity to improve health outcomes.

Together, these six review articles cover certain aspects of biomedical research on metabolic hormones and beyond. The reviews covered expanded functional analysis of GLP-1 and its based therapeutic agents to the clinical investigations that led to the first FDA approved hormone based drug, Rezdiffra, for MASLD. We anticipate seeing future success in making certain GLP-1 and FGF21 derivatives or further modified derivatives into future drugs for MASLD and other metabolic disorders. The reviews covered the role of bile acids in metabolic diseases in general to the specific perspective view on targeting bile acids themselves and beyond in expanding our healthspan and lifespan. It is worth mentioning that although scientists have not reached the common acceptance yet that bile acids are hormones, bile acids do mimic the physiological features with metabolic hormones, utilizing GPCRs as their receptors and exerting their systematic functions on multiple organs (from liver to gut and virtually any organ) [10]. Another important take home message is that organ-organ communications are fundamentally important in understanding function of hormones and pathophysiology of metabolic diseases. Indeed, we need to pay more and more attention to the gut, where metabolic hormones including GLP-1 are produced, where bile acids are processed, and where the dynamic changes on gut microbiota occur [9, 27, 28]. Finally, we need to pay more attention to the metabolic function of sexual hormones. The knowledge generated on metabolic functional studies on sexual hormones will not only advance our understanding of gender difference in various metabolic diseases, but may also lead to novel therapeutic strategies in personalized medicine.

Acknowledgments: I thank Canadian Institutes of Health Research (CIHR), Juvenile Diabetes Research Foundation (JDRF), Banting and Best Diabetes Centre (BBDC) for funding the lab (including lab personnel) in conducting our bench work investigation on GLP-1 and other hormones.

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