OVERVIEW

Peripheral actions of GPCRs in energy homeostasis: view from the Chair

M Bouvier

The roles of G-protein-coupled receptors (GPCRs) in the control of food intake and energy expenditure are being increasingly recognized, and new drug candidates targeting these receptors are making their entry into the clinic. GPCRs exert their action along the various sites of regulation of energy homeostasis control including the central nervous system, the pancreas, the gut and fat cells. Exciting new data about GPCRs recognizing and mediating the effects of lipid mediators and concerning receptors for which no endogenous ligands have been identified yet open new exciting avenues for the validation of additional drug targets. In addition, recently developed paradigms around the concepts of cross-talk regulation and functional selectivity should lead to the development of drugs with improved therapeutic efficacy and reduced undesirable effects. Some of these promising discoveries are discussed in the present article and accompanying papers.

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G-protein-coupled receptors (GPCRs) represent the largest family of membrane proteins involved in signal transduction across biological membranes.¹ They recognize a vast diversity of stimuli including neurotransmitters, hormones, chemokines and metabolites. As such, they have central roles in the control of a vast diversity of physiological functions, and they are the targets for many drugs that are currently being used or being developed for the treatment of many disorders.

Energy homeostasis is not an exception, and many GPCRs have been shown to regulate various elements of energy balance, and thus they are actively sought pharmacological targets for the treatment of metabolic disorders such as obesity and type-2 diabetes.^{2–6} These include receptors expressed in the central nervous system (ex: melanocortin type 1 and type 4, cannabinoid type 1, ghrelin and melatonin type 1 receptors) that may control appetite and/or energy expenditure, receptors localized on pancreatic cells (for example, glucagon-like peptide-1, gastric inhibitory peptide, melatonin type 1 and ghrelin receptors) controlling glucagon or insulin secretion or receptors present on fat cells (for example, β_3 adrenergic, niacin and succinate receptors) regulating lipolysis. In recent years, an increasing number of receptors that selectively recognize fatty acids and that are localized on pancreatic cells, adipocytes or in the gastrointestinal system (GPR40, GPR41, GPR83, GPR119 and GPR120) have been considered as potential therapeutic targets for obesity and related diseases. In particular, the role of some of these receptors (GPR40 and GPR119) in inhibiting glucose-stimulated insulin secretion has attracted considerable attention for the treatment of type-2 diabetes. In addition to receptors for which endogenous ligands are known and often well characterized, a number of orphan receptors for which no known ligand has been identified but are genetically linked to obesity are also considered as potential therapeutic targets for severe obesity and type-2 diabetes (for example, GPR21, GPR39, GPR82 and GPR101).

Despite the intense research carried out in recent years on GPCRs involved in energy balance, much remains to be done to offer new therapeutic solutions for metabolic diseases. For instance, no efficient pharmacological treatment exists yet for severe obesity. Promising results with new compounds targeting GPR40 (fasiglifam)⁷ and the glucagon-like peptide-1 (GLP-1) receptor (exenatide, liraglutide)⁸ in the treatment of type-2 diabetes raises hope and will certainly spur activity around the development of new drugs targeting different GPCRs for this indication.

Very recent breakthroughs in the elucidation of GPCRs' three-dimensional structure will be a significant booster for both fundamental research on the structure–function relationship of these receptors and for the rational design of compounds targeting them. In the past 6 years, more than 50 distinct crystal structures for more than 20 different receptors in their agonist, antagonist or unliganded forms have been solved, and the explosion of structural work shows no signs of slowing down.⁹ The resolution of the structures for some of the receptors targeted for type-2 diabetes and obesity treatments will be a welcomed source of information for the search of more selective and efficient drugs targeting either their orthosteric or allosteric sites. Another intense field of research that is likely to influence the search for better obesity-targeting drugs is linked to the concept of functional selectivity. In contrast to what was originally believed, GPCRs do not function as toggle switches that turn on or turn off a single signalling pathway but rather they can selectively engage different subsets of effectors including both G-protein-dependent and -independent pathways. Ligands can therefore activate some signalling cascades while inhibiting or sparing other signalling cascades coupled to a given receptor. This phenomenon known as ligand-biased signalling has obvious implications for the development of better drugs that could selectively target signalling modes that are relevant for the wanted therapeutic

activity without the undesirable effects resulting from other pathways.^{10,11}

Marc Caron, the plenary speaker of the symposium, addressed the potential clinical implications that the shift in paradigm resulting from the discovery of functional selectivity of GPCR could have for drug discovery. Using the D1 and D2 dopamine receptors as examples, he clearly demonstrated that ligands that selectively activate β -arrestin- vs G-protein-dependent signalling cascades have distinct behavioural consequences that could impact the development of new anti-schizophrenic drugs. Sheila Collins for her part introduced yet another level of complexity in the signalling activities regulated by GPCRs. She described the coordinated action of β -adrenergic and natriuretic receptors in the regulation of fat metabolism in adipocytes with a focus on the role of brown adipose tissue. Da Young Ho focused her talk on the promising GPR120 as a target for type-2 diabetes and inflammatory diseases. She showed how this receptor of omega-3 fatty acid expressed in both macrophages and adipocytes can mediate potent anti-inflammatory and insulin-sensitizing effects. Finally, Laurence Miller discussed the potential development of small molecules targeting one of the incretin receptors: the GLP-1 receptor in the treatment of type-2 diabetes. He reviewed some of the recent data about the binding mode of GLP-1 that should help the rational design of better compounds that could advantageously replace the already available peptide-based drugs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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