Special Issue: Metabolism Through the Lens of GPCRs

Opinion

Metabolic Actions of the Type 1 Cholecystokinin Receptor: Its Potential as a Therapeutic Target

Laurence J. Miller[1,*] and Aditya J. Desai[1]

Cholecystokinin (CCK) regulates appetite and reduces food intake by activating the type 1 CCK receptor (CCK1R). Attempts to develop CCK1R agonists for obesity have yielded active agents that have not reached clinical practice. Here we discuss why, along with new strategies to target CCK1R more effectively. We examine signaling events and the possibility of developing agents that exhibit ligand-directed bias, to dissociate satiety activity from undesirable side effects. Potential allosteric sites of modulation are also discussed, along with desired properties of a positive allosteric modulator (PAM) without intrinsic agonist action as another strategy to treat obesity. These new types of CCK1R-active drugs could be useful as standalone agents or as part of a rational drug combination for management of obesity.

CCK Regulation of Appetite

Obesity is a global public health problem also responsible for the epidemic increase in type 2 diabetes mellitus and related comorbidities and mortality [1,2]. Nutritional homeostasis and energy expenditure are perturbed in obesity and understanding the mechanisms that control food intake is critical in efforts to develop therapies to manipulate appetite and **satiety** (see Glossary). The gastrointestinal tract plays a central role in nutritional homeostasis as a site of caloric assimilation but also as a key regulator of appetite and energy balance, with these functions contributing to the establishment and maintenance of body weight. The gut accomplishes its regulatory roles through an intrinsic neuroendocrine system comprising cells that secrete regulatory peptides in response to luminal contents, which are distributed along the gastrointestinal tract and provide feedback to control key digestive events to optimize digestion and nutrient absorption [3].

A role for a parenterally administered intestinal extract to reduce food intake was first demonstrated in 1937 [4] and CCK, an intestinal peptide, was the first purified factor shown to elicit this effect, in 1973 [5]. Subsequently, CCK-like peptides, peptoids, and non-peptidyl agonists have confirmed their ability to reduce food intake in multiple species, including humans [6]. This effect was further corroborated by the observation that a **CCK1R** antagonist increased food intake in rodents [7,8] and by a genetic defect in CCK1R processing that resulted in obesity [9].

CCK exists as a family of different length peptides that share a carboxyl-terminal octapeptide amide known to contain the **pharmacophoric domains** critical for recognition by CCK1Rs and

Trends

Cholecystokinin (CCK), acting though the type 1 CCK receptor (CCK1R) on vagal afferent neurons, is an important physiologic regulator of appetite. While potent receptor agonists have been developed, they have not reached clinical use due to limited efficacy and potential side effects and toxicity.

Activation of CCK1R stimulates multiple interacting signaling cascades initiated through the G_q family, G_{13}, G_s, and arrestin. Biased agonists can potentially stimulate a subset of events responsible for satiety independent of events contributing to trophic and other side effects.

Positive allosteric modulators without intrinsic agonist activity can potentially enhance the satiety effect of endogenous CCK-58 released during a meal, reducing meal size and extending intermeal intervals.

New types of CCK1R-active drugs may be useful as standalone agents or as part of rational drug combinations.

[1]Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Scottsdale, AZ, 85259, USA

*Correspondence: miller@mayo.edu (L.J. Miller).

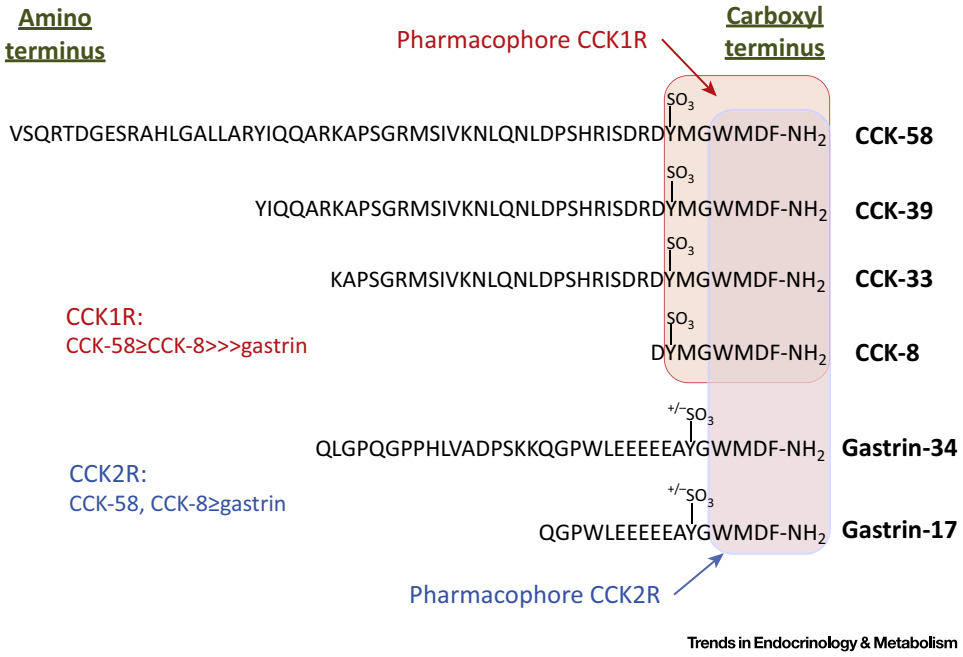

Figure 1. Structural Relationship between Cholecystokinin (CCK) and Gastrin Ligands and Type 1 CCK Receptor (CCK1R) and Type 2 CCK Receptor (CCK2R) Pharmacophores. Shown are naturally occurring forms of CCK and gastrin peptides sharing carboxyl-terminal amide sequences. Highlighted in blue and red, respectively, are the minimal fragments necessary and sufficient for high-affinity binding and potent biological responses at CCK2R and CCK1R (pharmacophoric regions).

type 2 CCK receptors (CCK2Rs) (Figure 1). CCK and gastrin share their carboxyl-terminal pentapeptide amide, with both peptides recognizing CCK2R (gastrin receptor) with similar high affinities and potencies. CCK1R, however, requires the unique amino-terminal extension present only in CCK, including a sulfated tyrosine, for high-affinity binding and full biological activity. CCK peptides are synthesized in neuroendocrine cells scattered throughout the mucosa of the proximal intestine and are secreted in response to fat and protein in the lumen. Classical targets for this hormone are CCK1Rs present in the gallbladder, pancreas, and pylorus, where they facilitate optimal food absorption by contributing to micelle formation, stimulating delivery of lipolytic and proteolytic enzymes and titrating the rate of delivery of nutrients to the absorptive surface. In addition to these classical digestive events, this hormone also acts on CCK1Rs present on vagal afferent neurons within the wall of the gastrointestinal tract, with these ultimately activating central nervous system neurons, including the nucleus of the solitary tract, important for appetite regulation [10].

The well-established activity of CCK to control appetite through peripheral receptors was the basis for active agonist drug development programs for the management of obesity by major pharmaceutical companies. Multiple candidates have been identified, with some entering clinical trials [11,12]. However, none of these agents has reached approval for clinical use, and all such programs seem to have been terminated because the therapeutic endpoint, defined as having greater effect on body weight than acute dieting and lifestyle modifications, was not met. There has also been concern that highly potent CCK1R agonists with long duration of action might exhibit side effects of abdominal cramping, nausea, and diarrhea, as well as the possibility of trophic effects that could contribute to progression of pancreatic cancer [13]. The regulatory bar for safety and efficacy is quite high for such drugs, since they are likely to be administered to relatively healthy people for long periods of time.

Glossary

Ago-positive allosteric modulator (PAM): ligand that possesses both agonist activity (capable of stimulating a biological response) and the ability to enhance the biological response to another agonist, most often the natural hormonal stimulant of the receptor.
Allosteric site: site within a receptor where an allosteric ligand can dock that is topographically distinct from where the natural hormonal ligand docks, providing the opportunity for both allosteric and orthosteric ligands to bind to the receptor simultaneously. This provides an opportunity to modulate the binding and/or action of the orthosteric agonist.
Biased agonist: receptor ligand that stimulates a set of signaling events and biological responses that is distinct (often a subset) of the spectrum of such events stimulated by the natural agonist.
Full agonist: receptor ligand capable of stimulating the full spectrum (and intensity) of signaling events and biological responses stimulated by the natural hormonal agonist.
G protein-coupled receptor (GPCR): the most common membrane receptor; possesses seven transmembrane helical segments that come together to form a bundle and transduces signaling events in the cell through interaction at its cytosolic face with a heterotrimeric G protein.
Lateral allosterism: impact on a membrane receptor coming from within the lipid bilayer, likely to be mediated through the outside of the helical bundle of a GPCR.
Orthosteric site: site of docking of an endogenous natural hormonal ligand to a receptor.
Partial agonist: receptor ligand capable of stimulating only submaximal signaling or biological response relative to the natural hormonal agonist.
Pharmacophoric domain: portion of a ligand or receptor that is responsible (adequate and sufficient) for its binding and/or biological activity.
Positive allosteric modulator (PAM): ligand that interacts with a receptor at a site that is spatially distinct from that where the natural hormone binds and that enhances