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Cholecystokinin (CCK) and related adjunct peptide therapies for the treatment of obesity and type 2 diabetes

Varun Pathak, Peter R. Flatt, Nigel Irwin*

SAAD Centre for Pharmacy and Diabetes, Ulster University, Coleraine, Northern Ireland, BT52 1SA, UK

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ABSTRACT

Cholecystokinin (CCK) is a hormone secreted from I-cells of the gut, as well as neurons in the enteric and central nervous system, that binds and activates CCK-1 and CCK-2 receptors to mediate its biological actions. To date knowledge relating to the physiological significance of CCK has predominantly focused around induction of short-term satiety. However, CCK has also been highlighted to possess important actions in relation to the regulation of insulin secretion, as well as overall beta-cell function and survival. Consequently, this has led to the development of enzymatically stable, biologically active, CCK peptide analogues with proposed therapeutic promise for both obesity and type 2 diabetes. In addition, several studies have demonstrated metabolic, and therapeutically relevant, complementary biological actions of CCK with those of the incretin hormones GIP and GLP-1, as well as with amylin and leptin. Thus, stable CCK derivatives not only offer promise as potential independent weight-reducing and glucose-lowering drugs, but also as effective adjunctive therapies. This review focuses on the recent and ongoing developments of CCK in the context of new therapies for obesity and type 2 diabetes.

1. Introduction

According to the World Health Organisation's (WHO) 2016 report, the number of people with type 2 diabetes and obesity has quadrupled in the last three decades, with estimates of around 600 and 422 million confirmed cases of obesity and diabetes worldwide. This represents a huge burden in terms of societal health, and associated escalating costs for treatment and management of the diseases and related complications, commonly termed diabesity [1]. As such, there is a clear need to develop novel and more effective anti- obesity and -diabetic drug options. In this regard, modified enzyme-resistant and longer-acting gut derived hormones have shown great therapeutic promise for diabesity [2]. This is clearly evidenced by the swift uptake of glucagon-like peptide-1 (GLP-1) receptor agonists into the diabetic clinic [3,4]. In addition, the GLP-1 drug, liraglutide, has been recently approved for the treatment of obesity [5]. Despite this, the ability of GLP-1 drugs to manage weight and regulate diabetes control have not been as successful as first envisaged from preclinical studies [6]. Thus, the therapeutic potential of other gut-derived hormones, such as cholecystokinin (CCK), is actively being explored [7]. There is also encouraging preliminary data with CCK that points towards enhancement of the biological actions of various related regulatory peptide hormones, including GLP-1 [8,9]. Therefore, this review will focus on the main biological and therapeutics actions of CCK, as well as combinational therapeutic approaches that incorporate CCK.

1.1. Cholecystokinin (CCK)

CCK was first discovered in 1928, when Ivy and Oldberg demonstrated that fluid extracts derived from the upper intestinal mucosa were able to instigate gallbladder contraction in pigs, dogs and guinea-pigs [10]. Indeed, until the mid-1900's CCK, along with gastrin and secretin, were largely regarded as a family of related peptides with a sole purpose of regulating digestion. However, other prominent physiological actions of CCK have now been revealed and include a role in fertility [11], inflammation [12], cardiovascular function [13], satiety [14], inhibition of gastric acid secretion [15] and stimulation of insulin secretion [16].

In keeping with a key physiological role for CCK, its amino acid sequence, characterised by the presence of a specific C-terminal pentapeptide sequence namely, Gly-Trp-Met-Asp-Phe-NH_2, is highly conserved throughout the animal kingdom from protochordates right through to humans (Fig. 1). CCK is chiefly secreted from enteroendocrine I-cells of the gut in response to feeding, particularly fat and proteins [17]; however, some enteric and central neurons can also release measurable amounts of CCK [14,18]. I-cells are principally located in

* Corresponding author.
E-mail address: n.irwin@ulster.ac.uk (N. Irwin).

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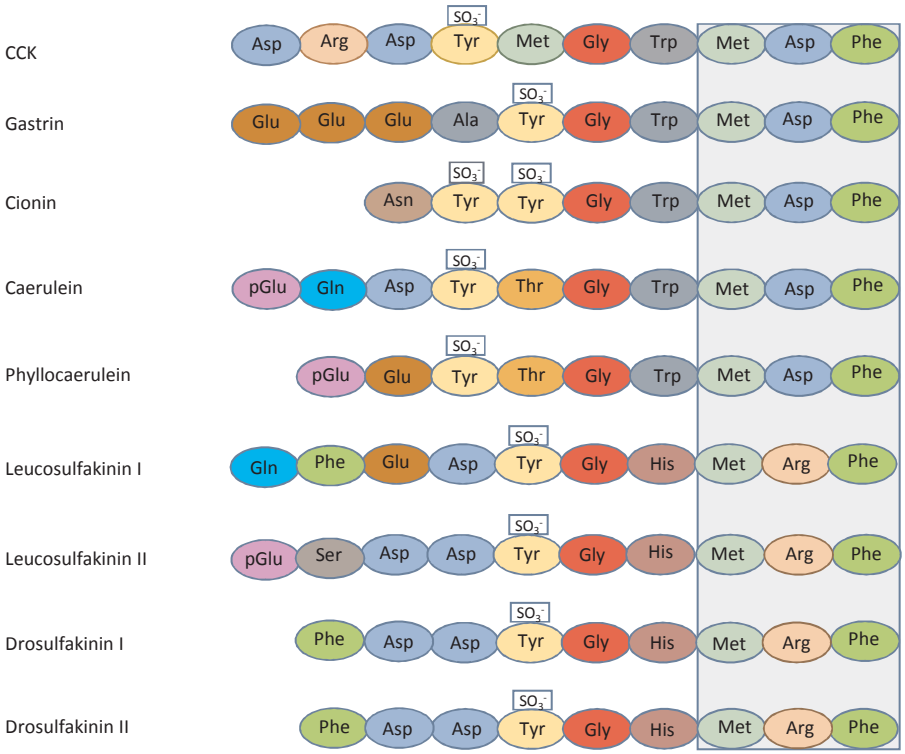

Fig. 1. Homologous amino acid sequences of CCK and other structurally related peptides from the animal kingdom. Cionin is a protochordate derived peptide, whilst Caerulein and Phyllocaerulein are found in frog skin secretions. Leucosulfakinin I, Leucosulfakinin II, Drosulfakinin I and Drosulfakinin II are insect peptides that structurally resemble CCK. All peptides possess sulphation(s) at each Tyr moiety and share the structurally conserved C-terminus penta-peptide sequence Gly-Xxx-Met-Asp-Phe, exemplifying common ancestral origin of human CCK and gastrin.

the duodenum and proximal jejunum in close proximity to enteroendocrine K-cells that secrete the incretin hormone glucose-dependent insulinotropic polypeptide (GIP) [2], with flow cytometry studies also revealing co-localisation of I-cells with GLP-1 producing L-cells in more distal gut regions [19]. In addition, more recent evidence has shown that the GLUTag cell line, widely used as an intestinal L-cell model to examine the effects of compounds on GLP-1 secretion, secretes significant amounts of CCK [20]. In harmony with this, it has also been demonstrated that enteroendocrine K-cells that principally secrete GIP, can also release substantial amounts of CCK [21]. Furthermore, the enteroendocrine STC-1 cell line, originally characterised as a CCK-producing I-cell model, also expresses and secretes a wide range of gut hormones including GIP and GLP-1 [22]. In humans, plasma concentrations of CCK are in the low picomolar range and increase 10–20 fold postprandially [23].

CCK is encoded by *cck* gene located on chromosome 3, and is initially synthesised as 115 amino acid gut derived preprohormone [24]. CCK is then post translationally processed to yield various truncated circulating forms including CCK-8, CCK-33 and CCK-58 peptides [25]. The biological actions of CCK peptides are triggered by the activation of specific CCK receptors, namely CCK-1 and CCK-2 (Table 1), with the latter often referred to as the gastrin receptor [26]. CCK-1 receptors are mainly present in peripheral tissues with CCK-2 receptors found centrally, and each receptor possesses specific ligand sequence selectivity (Table 1). As such, activation of the CCK-1 receptor requires a carboxyl-terminal heptapeptide-amide including a sulphated tyrosine residue, while CCK-2 receptors only require the conserved carboxyl-terminal tetrapeptide sequence that is common to all CCK and gastrin peptides [27]. CCK-8 is therefore the smallest form of CCK that retains activity at the level of the CCK-1 receptor (Fig. 1, Table 1).

1.2. Physiological actions of CCK

The key physiological role of CCK is believed to revolve around short-term regulation of energy intake [28], with obvious therapeutic implications for obesity/diabetes. Thus, a dose-dependent inhibition of food intake by CCK in rodents was first demonstrated in 1973 by Gibbs and co-workers [29]. Similar appetite suppressive effects were later demonstrated in pigs [30], rhesus monkeys [31] as well as in humans [32]. To delineate the specific receptor subtypes involved in CCK-mediated appetite suppressive effects, studies have utilised the CCK-1 receptor antagonist, devazepide, and CCK-2 receptor antagonist, L-365,260, in rodents and humans [33,34]. Current understanding suggests that CCK stimulates CCK-1 receptors on a subgroup of visceral afferent nerves that send satiety signals to the hypothalamus [35]. Thus, peripheral administration of CCK is believed to activate enteroendocrine CCK receptors, which transmit satiety signals to the hypothalamus via the vagus nerve [36]. There is also a suggestion that CCK-1 receptor activation stimulates secretion of the adipocyte-derived hormone, leptin, which also helps control energy intake [37]. Other

Table 1
Overview of the ligands, distribution and biological activity of CCK receptors.

	CCK-1 receptor	CCK-2 receptor
Potency	Caerulein > CCK-8 > gastrin > CCK-4	Caerulein > CCK-8 − gastrin − CCK-4
Antagonist	Proglumide, Lorglumide, Devazipide, Dexloxiglumide, Asperlicin	Proglumide, CI988, L365260, YF476
Agonists	CCK-8, CCK-33, Caerulein, SR146131, A71623	CCK-4, CCK-8, CCK-33, CCK-58, Gastrin, BBL454, L740093
Distribution	Gallbladder, intestine, pancreas, vagus nerve, nucleus tractus solitaries, area postrema, nucleus interpeduncularis	Cerebral cortex, nucleus caudatus, anterolateral nucleus accumbens, stomach, vagus nerve
Function	Pancreatic enzyme secretion, gall bladder contraction, stomach wall contraction, acute satiety, insulin release	Neurotransmission, regulation of anxiety, fear, locomotion, regulation of dopamine activity, moderating GABA release, increase neuronal firing rate