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Role of cholecystokinin in satiation: a systematic review and meta-analysis

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Abstract

The aim of this review was to examine: (1) the ability of cholecystokinin (CCK) or analogues of CCK to influence satiation and changes in body weight generally and (2) the efficacy of CCK in influencing satiation and eating behaviour specifically at physiological levels of dosing. A systematic review of the literature was performed following the PRISMA 2020 guidelines in five electronic databases investigating the effect of exogenous CCK or analogues on satiation and body weight. A meta-analysis of studies that infused CCK and measured satiation via changes in food/energy intake was also conducted. A total of 1054 studies were found using the search terms which were reduced to fifteen studies suitable for inclusion. Of the twelve studies measuring the effect on the weight of food ingested or energy intake, eleven showed a decrease. An analogue of CCK which can be administered orally failed to produce any weight loss at 24 weeks. The meta-analysis found the effect of CCK on satiation dosed at physiological levels was significant with a standardised mean difference of 0·57 (95 % CI 0·30, 0·85, $P < 0·0001$). By comparison, CCK dosed at higher, pharmacological levels also had a significant effect with a standardised mean difference of 0·91 (95 % CI 0·46, 1·36, $P < 0·0001$). Eight of the ten studies in the meta-analysis combined CCK infusion with some means to facilitate stomach distension. The present review found evidence that at both physiological and pharmacological levels of dosing CCK has a significant effect on satiation but no evidence for weight loss over the long term.

Key words: **Cholecystokinin: Satiation: Weight loss: Meal termination: Digestive peptides: Hormones**

Obesity and overweight are becoming increasingly common in both developed and developing nations globally. These conditions represent an important risk factor for mortality and morbidity from CVD, diabetes, cancers and musculoskeletal disorders, causing nearly three million annual deaths worldwide[1]. Despite clinical recommendations to prioritise lifestyle modification, a significant proportion of patients seeking therapies for weight loss will attain only modest weight loss from lifestyle modification[2]. This could be due to the development of the leptin resistance commonly found in overweight and obese individuals[3]. Thus, for individuals where conventional therapies such as diet and exercise have failed, pharmacotherapy may be seen as an additional option[4]. Examples of weight loss medications which are approved by the US FDA and available in the market include phentermine, orlistat, phentermine/topiramate extended release, lorcaserin, naltrexone sustained release/bupropion sustained release and liraglutide[5].

Satiation refers to physiological responses to food intake during the consumption of food which leads to a cessation of eating, whereas satiety refers to physiological responses which delay the taking of the next meal. The actions of digestive peptides form a key feature of the energy regulation system in humans[6] and their function in this system includes a major role in satiation and satiety signalling after the ingestion of a meal[7]. No relationship has been established between the number of eating episodes and body weight[8,9]; therefore, any potential dysfunction in the human energy regulation system in the contemporary food environment, should it exist, is more likely to be found within the biological processes which govern the regulation of meal size, that is, satiation[10].

Cholecystokinin (CCK) was one of the first digestive peptides to be discovered[11] and was subsequently shown to play an important role in the appetite control in animal models[12]. CCK is produced in the small intestine with the highest tissue concentration in the proximal section[13] and its release is mediated by the presence of protein and fat in the digestive tract[11]. CCK receptors are located in the pancreatic nerves, the gallbladder muscularis, the nerves and muscle along the gastrointestinal tract and several areas of the brain[14].

Abbreviation: CCK, cholecystokinin.

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At physiological levels, the release of CCK into the blood stream acts on CCK receptors causing gastric emptying to slow[15] and increasing sensations of fullness[16]. Although CCK is released very quickly into the blood stream (15 min post-prandially)[17], it is also relatively quickly removed. The elimination half-life of the octapeptide variant of CCK is 18 min[18]; however, a multitude of variants and concentrations of bioactive CCK variants with larger molecules may remain elevated in the blood plasma for several hours after a meal in healthy human volunteers[19]. Due to its rapid entrance into the blood plasma and short period of action, any effect of CCK on eating behaviour is more likely to be found within a meal rather than between meals and is therefore known as the digestive peptide most associated with satiation.

CCK and a selection of its analogues have been proposed as a weight loss medication[20]. It is important to distinguish between research focusing on the use of CCK or analogues of CCK at pharmacological doses as a potential weight loss agent and research investigating the role of CCK at lower doses in the physiology produced by the enteroendocrine system. The present systematic review therefore aims to examine (1) the ability of CCK or analogues of CCK to influence satiation and changes in body weight generally and (2) the efficacy of CCK in influencing satiation and eating behaviour specifically at physiological levels as found in the blood plasma.

Materials and methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines[21]. The search strategy and criteria for inclusion and exclusion were specified in advance and documented in the priori review protocol registered with the International Prospective Register of Systematic Reviews PROSPERO (University of York), registration number CRD42020210963.

Search terminology

The search terms included the keywords: ('cholecystokinin' OR 'CCK') AND ('infusion' OR 'agonist' OR 'analog' or 'analogue') AND ('energy intake' OR 'weight loss' OR 'satiation' OR 'satiety'). Where databases allowed searching by Medical Subject Headings (MeSH), the terms 'Cholecystokinin' (MeSH) AND 'Energy Intake' (MeSH) OR 'Satiation' (MeSH) were also included.

Search strategy

The CINAHL, Cochrane Central Register of Controlled Trails, MEDLINE, Scopus and Web of Science databases were searched for all relevant publications (data cut off – July 2020, exclusion of non-human studies), using a combination of keywords and Medical Subject Headings to increase the sensitivity and inclusiveness of searches. The search architecture was designed by an expert systematic review librarian (M.T.). Search strategies are presented in the Appendix (online Supplementary material). The search strategy was validated by checking that pre-selected relevant studies were indeed retrieved by at least one of the database searches. The titles and abstracts of all retrieved studies were exported to *Covidence* (*Covidence systematic review software, Veritas Health Innovation,* Melbourne, Australia) for the study selection process.

Study selection

Randomised controlled trials on adult individuals that examined the effect of an intervention involving CCK or any pharmaceutical agent which mimics the actions of CCK on energy intake and/or change in body weight were included. Randomised crossover trials with a washout period of less than 1 d; diet studies; studies where subjects suffered from any metabolic disorder such as diabetes, studies on bariatric patients and patients taking a weight loss drug; studies where the primary focus was psychological; studies where the primary focus was exercise; studies with participants taking a psychiatric medication and studies where participants were taking a pharmaceutical other than CCK or a CCK agonist which may affect hunger; and non-human studies were all excluded. The abstracts of articles deemed relevant by the lead author (A.W) were independently reviewed by a further investigator (N.N.). If consensus was not reached, the article was moved on to the next stage for a review of the full text. The full texts of the remaining eligible studies were independently reviewed by the investigators (A.W. and N.N.) against the inclusion and exclusion criteria. Any final discrepancies were resolved by referral to a third researcher (S.S.). Disagreements were discussed until consensus was reached in all cases.

Data extraction

Data were extracted from each study to be included and placed on spreadsheets. Information such as study title, study type, number of subjects, randomisation, degree of blinding, energy intake, appetite responses on a Visual Analogue Scale (VAS) and change to hormone levels was inputted into the spreadsheets.

Data synthesis

The primary means of data synthesis was the extraction of study data and extraction into pre-defined spreadsheets. The results were synthesised narratively for interpretation in the 'Discussion' section.

Data analysis

The review software (Review Manager (RevMan) (Computer program). Version 5.4.1, The Cochrane Collaboration) was used for the meta-analysis. The outcome to be assessed in the meta-analysis was the difference in mean between those treatments using CCK or CCK analogues and placebo. Data were qualitatively compared across the various methodological approaches of included studies to assess the efficacy of CCK to enhance satiation, reduce energy intake and facilitate weight loss.

Risk of bias and quality assessment

The Physiotherapy Evidence Database (PEDro) scale[22] was used to assess the quality of the methodology used in each of the studies included in this review. The PEDro scale is an

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eleven-item scale used to assess the eligibility criteria, randomisation process, allocation processes, similarity of baseline groups, the blinding process, completeness of data used, between group statistics and measures of variability of a study. Each study is allocated one point on the condition that it complies with one of the eleven items. One author assessed each study for bias (A.W.). The risk of bias for each of the studies was evaluated using criteria suggested by the Cochrane Collaboration[23] which equates to calculating the total score of PEDro items two to four and seven to nine. A score of five to six is considered to indicate a low risk of bias, a score of three to four moderate and one or two high.

Results

Study selection

Initially, a total of 1054 studies were identified, and after removal of 464 duplicates 590 abstracts remained. By screening based on a reading of study abstracts, a further 545 studies were excluded. The remaining forty-five studies were then independently reviewed by two researchers (A.W., N.N.) and following discussion a further thirty studies were removed to arrive at a final figure of fifteen studies for inclusion reached by consensus (see Fig. 1).

Study characteristics

The characteristics of the included studies are summarised in Table 1.

Participants

A total of 938 participants (404 male, 534 female) were used in the studies included in this review. All participants used in these studies were healthy and three studies utilised overweight or obese subjects[24–26].

Study designs

All of the studies included in this review were randomised controlled trials[16,24–37]. Two of the included studies were of a parallel design[24,36], while the remainder were crossover[16,25–29,31–33,37] or utilised a counterbalanced design[30,34,35]. All of the studies in this review were acute studies excepting one[24] which had a duration of 24 weeks. The primary aim of the studies included in this review was to investigate the effect on satiation occurring in response to exogenous CCK or an analogue of CCK. Interventions predominantly involved the use of an intravenous infusion of CCK[16,25–37] with a saline infusion as a control. One study[32] used a CCK receptor antagonist, loxiglumide, to negate the effect of CCK. Four studies compared the effects of CCK with another peptide such as GLP-1[28,33] or glucagon[30]. Two forms of CCK were utilised in infusions: CCK-8 and CCK-33. CCK-8 was used in nine of the studies[27–32,34,35,37] and CCK-33 in five studies[16,25,26,33,36]. One study[24] involved the use of an analogue of CCK (GI181771X) taken as a 0·25 mg, 0·5 mg, 1·0 or 1·5 mg dose in an oral solution three times daily.

Dosing ranged between infusions of a lower, or physiological dose[16,25–27,29,32,33], or higher, pharmacological doses[24,28,30,31,34–37]. Four studies utilised a preload prior to infusion such as banana shake[26,32], soup[31] or solid food such as cracker biscuits with topping and juice[34]. One study employed use of a gastric balloon in order to combine the stimulus of CCK with those of stomach distention[35].

The effect on satiation was measured by the difference in the weight of food consumed by participants[16,25,26,30,34,35] or the effect on energy intake[27–29,31–33] or subjective measures of satiety[16,25,26,28,29,31–33,36,37]. Three of the studies measured changes in hormone levels[24,29,33].

Risk of bias and quality assessment

According to the Cochrane Classification Risk Scale, four of the studies in this review were assessed as having a high risk of bias[24,30,33,35] with the remainder of the studies[16,25–29,31,32,34,36,37] assessed as having a moderate risk of bias. One study was single blinded[27], the remainder of the studies[16,24–26,28–33,36,37] were all reported to be double-blinded. The quality of the methodology used in the studies and risk of bias in studies is summarised in Table 2.

Effect on satiation and body weight

Of the twelve studies[16,26–35,37] measuring the effect on satiation via either a reduction in energy intake or the weight of food consumed, eleven studies[26–35,37] showed a significant effect, with only one study[16] showing no effect. Of the ten studies[16,25,26,28,29,31–33,36,37] measuring the effect on satiation via subjective appetite ratings, nine[25,26,28,29,31–33,36,37] showed a significant positive influence on measures of satiety with one[16] showing no effect. One study[24], utilising a CCK-A receptor agonist taken as an oral solution (GI181771X), showed no significant effect on body weight at 24 weeks. The effects of CCK on satiation and body weight are summarised in Table 3.

Meta-analysis

The question as to whether any effect from CCK on satiation is merely the result of pharmacological dosing and whether CCK is truly efficacious at levels in the blood plasma produced by the physiology is controversial[38]. A random effects model meta-analysis was employed to investigate this question. Nine studies in the present review infused CCK at doses facilitating a level of CCK in the blood plasma considered to be physiological[16,25–29,32,33,36]. Dosages used for each of these studies are shown in Table 1. Seven of the nine studies[16,26–29,32,33] measured satiation via the difference in the weight of food ingested or energy intake. Two of the nine studies[25,36] utilised only subjective measures of the effect on satiation using a VAS scale and were excluded from the meta-analysis. Five studies dosed CCK at pharmacological levels[30,31,34,35,37]. Data suitable for inclusion into the meta-analysis were available for three of these studies[31,34,37] which were added to the meta-analysis for comparison. In summary, studies which infused CCK at physiological levels of dosing had a significant effect with a standardised mean difference of 0·57 (95 % CI 0·30, 0·85, $P < 0·0001$) as did studies which infused CCK at pharmacological levels of dosing which has a standardised mean difference of 0·91 (95 % CI 0·46, 1·36, $P < 0·0001$). Both results were

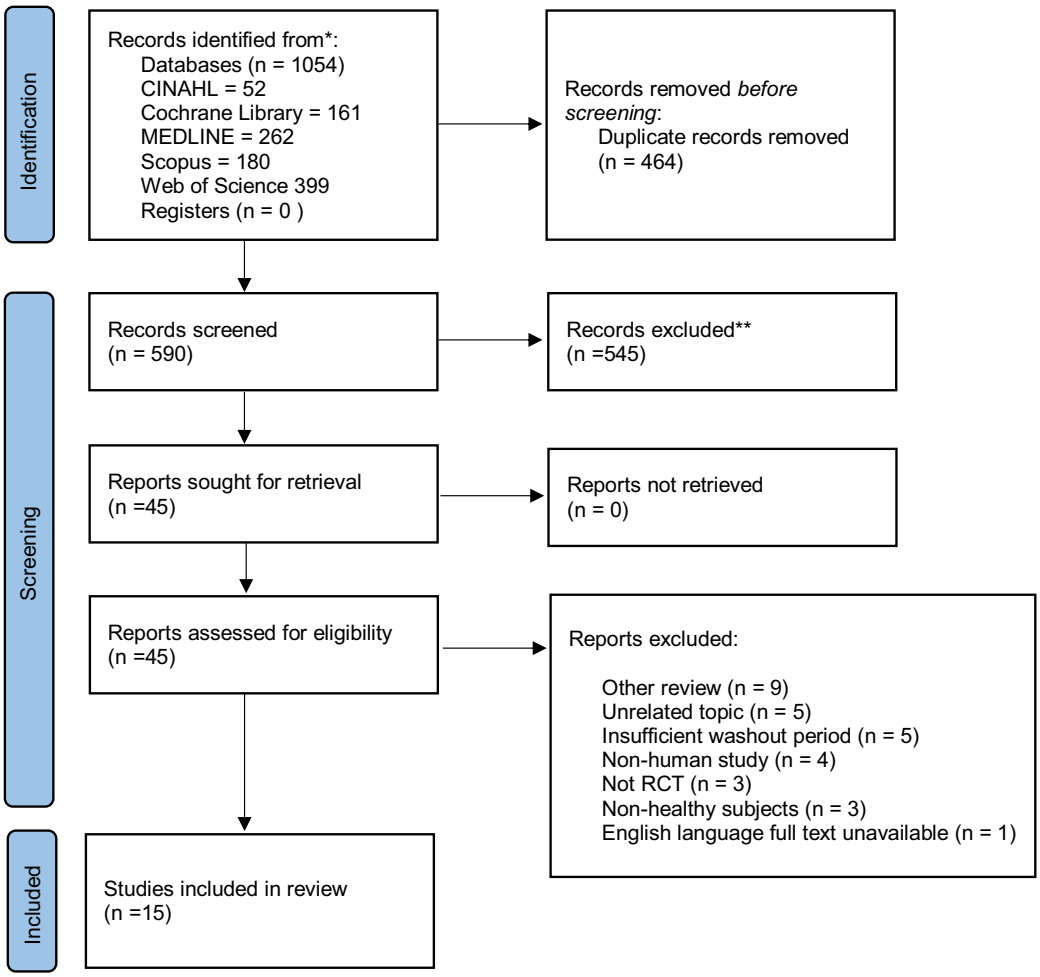

Fig. 1. Flow chart of study selection.

at a high level of homogeneity ($I^2 = 7\,\%$ and $0\,\%$, respectively). A sensitivity analysis was conducted excluding any studies originally included in the meta-analysis found to have a potentially high level of bias[33] and results remained significant with a standardised mean difference of 0·45 (95 % CI 0·15, 0·74, $P = 0{\cdot}003$). The results of the meta-analysis are shown in Fig. 2.

Discussion

Early research into the use of CCK produced conflicting evidence on satiation with some studies demonstrating efficacy[34,36,37] while others indicated no effect[16,39]. The present review found evidence indicating that exposure to exogenous CCK results in an increase in satiation. This was demonstrated in studies measuring satiation *via* reduction in food or energy intake or *via* an increase in subjective satiety measures and was the case for both the CCK-8 and CCK-33 variants of the peptide. Where observed, the reduction in food intake appears to result from earlier meal termination as opposed to a reduction in the rate of food intake[31,34]. These results were further supported by a finding of increased satiation in nine of the ten studies assessing satiation by subjective measures.

Attempts have been made to utilise CCK's effects on satiation by development of a viable pharmaceutical product for weight loss. One study[24] in this review involved the use of such a drug – the CCK-A receptor agonist GI181771X – which is available in an oral solution form. Use of GI181771X over a 24-week period failed to produce any effect on body weight[24]. The study's authors discounted CCK's use as a monotherapy for weight loss yet acknowledged a potential role for CCK in regulating energy intake. There may be multiple explanations for GI181771X's failure to facilitate weight loss. This study utilised overweight and obese patients, and it is possible that some other weight regulation pathways, such as the development of leptin resistance in participants, could have become involved and negated the effect of CCK agonist use. Tachyphylaxis could provide a further explanation. Another still may be an acute effect which is not sustained whether due to the short half-life of the molecule or a lower within-meal energy intake resulting in an increase in meal frequency. CCK-8 has been shown to significantly reduce pre-meal hunger and reduced energy intake at a subsequent *ad libitum* test meal[31]; however, the smaller meal resulted in a faster return of hunger if compared with placebo. It should be noted that the present review identified only one study which assessed the potential of a CCK analogue for weight loss and thus a

Table 1. Studies used in the systematic review

Paper	Study type	Intervention	CCK dosage	Additional stimulus	Control	Blinding	Washout	Subjects	Outcomes
Ballinger *et al.* 1995	Randomised crossover	I.V. CCK-8	40·0 ng/h per kg	200 ml water 5 min prior; 200 ml water with test meal	Saline	Single blind	> 1 week	4 males and 2 females	Energy intake
Brennan *et al.* 2005	Randomised crossover	I.V. CCK-8, I.V. GLP-1	2·0 ng/kg per min	Free intake of fluid (600 g of iced coffee and water served)	Isotonic saline	Double blind	3–10 d	9 males	Appetite, energy intake, gut motility
Brennan *et al.* 2008	Randomised crossover	I.V. CCK-8	0·33, 0·66 and 2·0 ng/kg per min	Free intake of fluid (600 g of iced coffee and water served)	Isotonic saline	Double blind	4–10 d	10 males	Gut motility, GI hormones, appetite, energy intake
Geary *et al.* 1992	Randomised counterbalanced	I.V. CCK-8, I.V. glucagon	2·0 or 3·0 ng/kg per min		Saline	Double blind	Unclear	16 males	Food intake
Greenough *et al.* 1998	Randomised crossover	I.V. CCK-8	4·0 ng/kg per min	Soup preload; large jug of water with test meal	Saline	Double blind	Unclear	15 males	Hunger, energy intake, anxiety, nausea
Gutzwiller *et al.* 2000	Randomised crossover	I.V. CCK-8, I.V. loxiglumide	0·75 μg at 1 ml/min over 10 min	400 ml banana shake preload; free intake of fluid with test meal	Saline	Double blind	≥ 7 d	32 males	Energy intake, hunger, satiety
Gutzwiller *et al.* 2004	Four-way randomised crossover	I.V. CCK-33, I.V. GLP-1	0·2 pmol/kg per min	Free intake of fluid with test meal	Saline	Double blind	≥ 7 d	24 males	Energy intake, hunger, fullness, blood glucose, hormone levels
Jordan *et al.*, 2008	Randomised, parallel arm	Solution of CCK-A agonist (GI181771X)	0·25, 0·5, 1·0 and 1·5 mg 3 times/d		Matching tablet placebo	Double blind	N/A	*n* 701 (234 males, 467 females)	Body weight, waist measures, blood sugar and lipids, insulin, blood pressure
Kissileff *et al.* 1981	Randomised, counterbalanced	I.V. CCK-8	4·0 ng/kg per min	Preload of crackers with topping and juice	Saline	Unclear	> 1 d	12 males	Food intake, meal duration
Kissileff *et al.* 2019	Randomised, counterbalanced	I.V. CCK-8 with gastric balloon	168·0 ng/min	Saline filled gastric balloon	Saline	Unclear	> 1 d	*n* 12 (5 males, 7 females)	Food intake
Lieverse *et al.* 1992	Randomised crossover	I.V. CCK-33	2·5 C.U./kg weight per 150 min		Saline	Double blind	> 1 week	*n* 18 (4 males, 14 females)	Satiety measures, food intake
Lieverse *et al.* 1994	Randomised crossover	I.V. CCK-33	1 ivy dog unit/kg weight per height		Saline (1 h infusion)	Double blind	> 1 week	*n* 32 (4 males, 28 females)	Satiety measures
Lieverse *et al.* 1995	Randomised crossover	I.V. CCK-33	1 ivy dog unit/kg weight per height	Standardised banana shake preload	Saline	Double blind	> 1 week	18 females	Satiety measures, food intake
Stacher *et al.* 1978	Randomised parallel	I.V. CCK-33 (95 % porcine)	180 ml/30 mins 0·6, 3·0 or 6·0 ivy dog units/kg		180 ml/30 min saline	Double blind	N/A	*n* 16 (8 males, 8 females)	Satiety measures
Stacher *et al.* 1981	Randomised crossover	I.V. CCK-8	1·5 or 3·0 ivy dog units/kg per 15 min		Saline	Double blind	> 1 d	*n* 16 (8 males, 8 females)	Satiety measures, food intake

CCK, cholecystokinin.

Table 2. Risk of bias table

Eligible studies	PEDro items											Total	Cochrane classification of risk of bias
	1	2	3	4	5	6	7	8	9	10	11		
Ballinger *et al.* 1995	1	1	0	0	1	0	0	1	1	1	1	7	3/6 (moderate)
Brennan *et al.* 2005	1	1	0	0	1	1	1	1	1	1	1	9	4/6 (moderate)
Brennan *et al.* 2008	1	1	0	0	1	1	1	1	1	1	1	9	4/6 (moderate)
Geary *et al.* 1992	1	1	0	0	1	1	1	0	0	1	1	7	2/6 (high)
Greenough *et al.* 1998	1	1	0	0	1	1	1	1	1	1	1	9	4/6 (Moderate)
Gutzwiller *et al.* 2000	1	1	0	0	1	1	1	1	1	1	1	9	4/6 (moderate)
Gutzwiller *et al.* 2004	1	1	0	0	1	1	1	0	0	1	1	7	2/6 (high)
Jordan *et al.*, 2008	1	0	0	1	1	1	1	0	0	1	1	7	2/6 (high)
Kissileff *et al.* 1981	0	1	0	0	1	1	1	1	1	1	1	8	4/6 (moderate)
Kissileff *et al.* 2019	1	1	0	0	0	0	0	0	0	1	1	4	1/6 (high)
Lieverse *et al.* 1992	0	1	0	0	1	1	1	1	1	1	1	8	4/6 (moderate)
Lieverse *et al.* 1994	0	1	0	0	1	1	1	1	1	1	1	8	4/6 (moderate)
Lieverse *et al.* 1995	0	1	0	0	1	1	1	1	1	1	1	8	4/6 (moderate)
Stacher *et al.* 1978	0	1	0	0	1	1	1	1	1	1	0	7	4/6 (moderate)
Stacher *et al.* 1981	0	1	0	0	1	1	1	1	1	1	1	8	4/6 (moderate)

1. Eligibility criteria were specific.
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received).
3. Allocation was concealed.
4. The groups were similar at baseline regarding the most important prognostic indicators.
5. There was blinding of all subjects.
6. There was blinding of all therapists who administered the therapy.
7. There was blinding of all assessors who measured at least one key outcome.
8. Measures of at least one key outcome were obtained from more than 85 % of the subjects initially allocated to groups.
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analysed by 'intention to treat'.
10. The results of between-group statistical comparisons are reported for at least one key outcome.
11. The study provides both point measures and measures of variability for at least one key outcome.

broader review including more such studies on this topic is likely warranted before drawing any conclusions. In any case, another drug in the same class as GI181771X (CCK-1 receptor agonist) has been found to produce abnormal effects on the exocrine pancreas[40] which would limit the future use of drugs in this class and GI181771X's proposed use as a potential weight loss drug has itself been discontinued by the developer[41].

The effects of CCK are known to be dose dependent[29]. As evidenced in the meta-analysis contained in the present review, at higher or pharmacological doses the weight of evidence

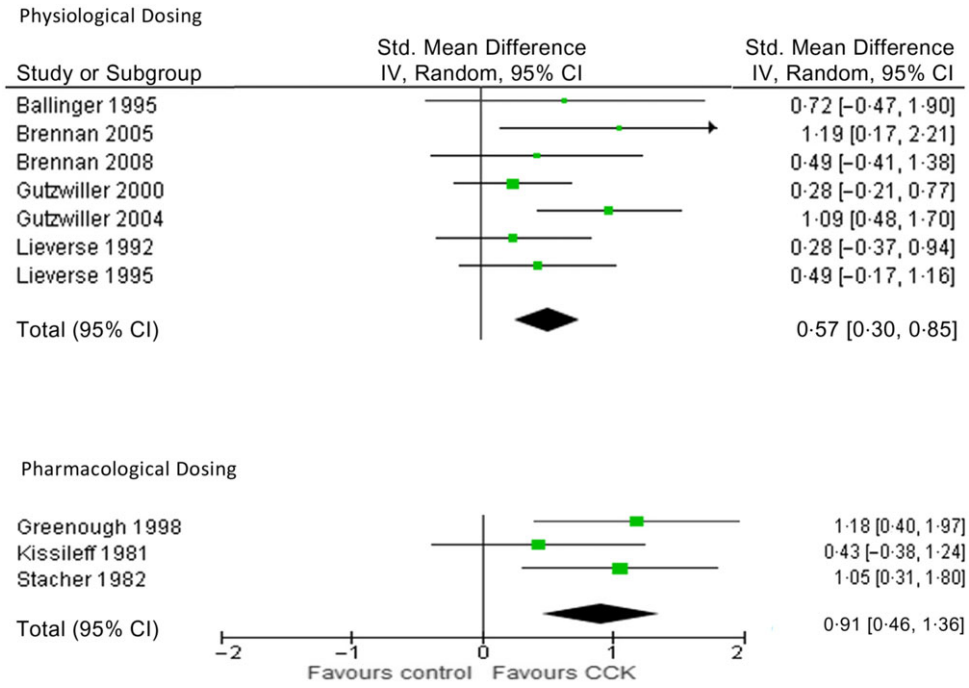

Fig. 2. Forest plot of standardised mean difference in effect of cholecystokinin on satiation at both physiological and pharmacological levels of dosing.

Table 3. Study outcomes

Paper	Intervention	VAS scale	Food/ energy intake	Hormone levels	Body weight	Other	Comment
Ballinger *et al.* 1995	I.V. CCK-8	N/A	Decrease	N/A	N/A	N/A	
Brennan *et al.* 2005	I.V. CCK-8, I.V. GLP-1	Increase	Decrease	N/A	N/A	Increase*	*CCK-8 increased the number and amplitude of isolated pyloric pressure waves and basal pyloric pressure
Brennan *et al.* 2008	I.V. CCK-8	Increase	Decrease	Increase**	N/A	Increase***	**CCK-8 increased PYY concentrations ***stimulated phasic and tonic pyloric pressures
Geary *et al.* 1992	I.V.CCK-8, I.V. glucagon	N/A	Decrease	N/A	N/A	N/A	
Greenough *et al.* 1998	I.V. CCK-8	Increase	Decrease	N/A	N/A	Decrease****	****Shortening of meal duration with an increase in pre-meal anxiety
Gutzwiller *et al.* 2000	I.V. CCK-8, I.V. loxiglumide	Increase	Decrease	N/A	N/A	N/A	Interaction between CCK-8 and preload was noted
Gutzwiller *et al.* 2004	I.V. CCK-33, I.V. GLP-1	Increase	Decrease	No effect^	N/A	Decrease^^	^No detectable difference between the plasma CCK concentrations after CCK-33 alone v. CCK-33 plus GLP-1 infusions. No difference between GLP-1 responses seen after infusion of GLP-1 alone compared with CCK-33 plus GLP-1 ^^after CCK-33 infusion blood glucose decreased
Jordan *et al.*, 2008	Solution of CCK-A agonist (GI181771X)	N/A	N/A	No effect^^^	No effect	No effect^^^^	^^^Insulin was similar in treatment group and placebo ^^^^GI181771X did not have a beneficial effect on serum total cholesterol, high density, lipoprotein cholesterol, LDL-cholesterol or TAG. HbA1c, fasting plasma glucose, fasting serum insulin, homoeostasis model assessment (HOMA) index and blood pressure data were similar in placebo and in GI181771X-treated patients
Kissileff *et al.* 1981	I.V. CCK-8	N/A	Decrease	N/A	N/A	Decrease~	~Shortening of meal duration
Kissileff *et al.* 2019	I.V. CCK-8 with gastric balloon	N/A	Decrease	N/A	N/A	N/A	Use of CCK-8 in conjunction with gastric balloon
Lieverse *et al.* 1992	I.V. CCK-33	No effect	No effect	N/A	N/A	N/A	No effect at physiological dose
Lieverse *et al.* 1994	I.V. CCK-33	Increase	Decrease	N/A	N/A	N/A	
Lieverse *et al.* 1995	I.V. CCK-33	Increase	Decrease	N/A	N/A	N/A	
Stacher *et al.* 1978	I.V. CCK-33	Increase	N/A	N/A	N/A	N/A	
Stacher *et al.* 1981	I.V. CCK-8	Increase	Decrease	N/A	N/A	N/A	

CCK, cholecystokinin.

clearly supports the case for an effect by CCK on satiation. Until now the case for an effect at physiological doses, however, has been less clear. This point is of relevance as any findings in relation to CCK's role in eating behaviour would apply to biological mechanisms only to the extent that dosing of CCK was similar to those levels found physiologically in the blood plasma.

Originally it was thought that the mechanism underlying CCK's effect on satiation was due to CCK's influence on gastric emptying. Subsequently, it was shown that CCK's effect on food intake was greater than that on gastric emptying[42] suggesting the existence of another mechanism. In rats, it was found that an infusion of CCK prior to the delivery of a gastric load significantly magnifies the response from fibres in the afferent vagus[43]. Other studies, both animal and human, have shown that gastric distention increases the reduction of food intake produced by CCK infusions[42,44]. The relationship between CCK dosage, gastric distension and the resulting level of food intake appears to be linear. A potential synergistic interaction between the effects of CCK and gastric distention has been studied, but this was not found to be significant[35]. Eight of the ten studies included in the meta-analysis[26–29,31–34] utilised some means to facilitate stomach distension. The one study which failed to find an effect of CCK on satiation[16] did not employ any means to increase stomach distention such as a preload. CCK has been

found to both reduce food/energy intake and increase subjective satiety measures at physiological levels when combined with a preload or gastric distension mediated by the use of a gastric balloon[35]. Four studies in the meta-analysis utilised a preload[26,31,32,34]. CCK has also been shown to reduce energy intake when accompanied by intragastric load of saline[45] and thus it was notable that studies which did not utilise a preload tended to incorporate a sizeable fluid intake into the test meal. Five studies allowed free intake of fluid together with the test meal[28,29,31–33]. A sixth[27] incorporated 200 ml of water intake 5 min prior to the test meal and a further 200 ml of water to be consumed together with the test meal.

The results of these studies suggest separate feedback systems working in unison to mediate satiation. A proper understanding of the function and efficacy of biochemical signalling from the consumption of food cannot be realised without considering input from multiple feedback systems[46] and, specifically in the present review, CCK in combination with stimulus from mechanical receptors in the stomach. Eating behaviour is governed by the body estimating energy intake based on input from multiple systems. Combining CCK or CCK analogues with stimulus from other feedback systems to better regulate energy intake may present a road for future research. However, the greatest value of these findings is their potential in further elucidating the complex systems which regulate energy intake.

Conclusion

The findings of this systematic literature review indicate that the exposure to either the CCK-8 or CCK-33 variants of CCK may result in an increase in satiation in healthy participants. This effect also appears to result from earlier meal termination rather than a reduction in the rate of food intake. An analogue of CCK which can be administered orally failed to produce any long-term weight loss at 24 weeks. The meta-analysis found that CCK has a significant effect on satiation at both physiological and pharmacological levels in the blood plasma.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114522000381

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