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Dairy-derived peptides for satiety

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ABSTRACT

Satiety hormones produced in the gastrointestinal tract are key players in influencing appetite and food intake. Dairy proteins that target these gastric signals have the potential to make one feel 'fuller for longer'. While effects of whey and casein on appetite and food intake are well documented, this review focuses on individual dairy peptides. The evidence of these peptide bioactives on satiety signaling *in vitro* using cellular models and *in vivo* via intervention trials is summarized. Dairy protein hydrolysates are also reviewed for their satiating properties. How their efficacy compares to other notable food derived peptides and how this efficacy can be lost, bolstered or protected during gut transit is also summarized.

1. Introduction

Food intake is strongly linked to appetite (Blundell, Dalton, & Gibbons, 2018). As we eat, peptide signals from the gut change our attitude to food from the "hunger" state to the "satiation" state, resulting in meal termination (Amin & Mercer, 2016). Arrival of food in the stomach causes its distention and stimulates the release of satiety signals. Satiety hormones are released from specialized enteroendocrine cells along the length of the gut (Gribble & Reimann, 2016). These hormones are the main connection between the gastrointestinal (GI) system and the appetite center of the brain (Kaelberer et al., 2018). Enteroendocrine cells account for less than 1% of all intestinal epithelial cells and their types differ by hormone secretion patterns and localization within the gut (Worthington, Reimann, & Gribble, 2018). Different enteroendocrine cells are capable of producing different gut hormones, depending on circumstance (location, diet and/or metabolic state). In general, I cells are found in the duodenum and jejunum and predominantly secrete the family of cholecystokinin (CCK) anorexigenic peptides (Chaudhri, Small, & Bloom, 2006). Once released, CCK peptides inhibit gastric emptying, improve secretion of insulin, somatostatin, digestive enzymes from the pancreas and bile from the gallbladder (Chaudhri et al., 2006; Pathak, Flatt, & Irwin, 2018). Other anorexigenic hormones, glucagon-like peptide-1 (GLP-1) and peptide YY (PYY) are secreted by L cells, which are predominantly localized in the ileum and colon (De Silva & Bloom, 2012; Holst, 2007). They suppress appetite by delaying gastric emptying, promoting pancreatic secretion and central nervous system signaling (Batterham et al., 2002). Ghrelinergic cells in the fundus of the stomach secrete a unique orexigenic hormone, ghrelin, responsible for the feeling of hunger and feeding behavior (De Graaf, Blom, Smeets, Stafleu, & Hendriks, 2004). Many gut hormones undergo some form of post transcriptional modification to become active (e.g. CCK has active forms CCK-58, CCK-33, CCK-22 and CCK-8) and have short circulating lifetimes (e.g. 2–5 min for active GLP-1 (7-36) and GLP-1 (7-37)). In fact the endogenous peptidase, dipeptidyl peptidase-IV (DPP-IV) can cleave active GLP-1 forms so that up to 75% of GLP-1 is inactivated before leaving the GI tract (Chaudhri et al., 2006; Baggio & Drucker, 2007; Holst & Deacon, 2005). Other satiety hormones include gastrin-releasing peptide and oxyntomodulin, although their properties are less well defined (Cummings & Overduin, 2007). In addition, other gut hormones with a board spectrum of biological responses such as somatostatin, endogenous opioids, leptin and serotonin, all interact with satiety and appetite signaling cascades (Pupovac & Anderson, 2002; Wei et al., 2018; Worthington et al., 2018). For example, heterodimerization of G-coupled protein receptors (GCPR) facilities crosstalk between ghrelin and serotonin pathways (Schellekens et al., 2015). Insulin which is tightly linked to blood glucose concentrations is in turn regulated by GLP-1 and gastric inhibitory polypeptide (GIP).

Abbreviations: AA, amino acid; α-LA, α-lactalbumin; β-CM7, β-casomorphin-7; β-LG, β-lactoglobulin; BSA, bovine serum albumin; CCK, cholecystokinin; CMP, caseinomacropeptide; DPP-IV, dipeptidyl peptidase-IV; GCPR, G-coupled protein receptors; GI, gastrointestinal; GIP, gastric inhibitory polypeptide; GMP, glycomacropeptide; GLP-1, glucagon-like peptide-1; GRAS, generally regarded as safe; GRP, gastrin releasing peptide; GSPE, grape-seed procyanidin extract; Ig, immunoglobulin; I.p, intraperitoneal; Lf, lactoferrin; PYY, peptide YY; VAS, visual analogue scale; WPC, whey proteinconcentrate; WPI, whey protein isolate; WSE, water soluble extract

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Since satiety hormone secretion is governed by food, appetite suppressing bioactive compounds from foods offer an attractive alternative to pharmacological solutions to control appetite, over one's lifetime. For example, epidemiological studies demonstrate that consumption of dairy foods, especially low fat dairy, milk and yogurt can help to maintain a healthy body weight (Dougkas, Reynolds, Givens, Elwood, & Minihane, 2011; Feeney et al., 2017; Sayon-Orea, Martínez-González, Ruiz-Canela, & Bes-Rastrollo, 2017). In addition, consumption of dairy proteins may enhance efficacy of appetite suppressing drugs. For example, intraduodenal infusions of milk protein concentrate increased the effectiveness of sitagliptin, a pharmacological inhibitor of DPP-IV (Olivos et al., 2014). However the link between dairy consumption, food intake and weight loss is not without controversy. Intervention trials with dairy products consumption, however without energy restriction, often do not lead to weight loss (Lanou & Barnard, 2008). What is accepted, is that proteins are generally regarded as more satiating than other macronutrients (Morell & Fiszman, 2017). Small peptides and amino acids (AAs) act via GCPR receptors, elevating intracellular Ca^{2+} and/or cAMP concentrations, or via peptide/AA transporters, which depolarize the enteroendocrine cell membrane, triggering Ca^{2+} influx and activating satiety hormones secretory mechanisms (Tolhurst, Reimann, & Gribble, 2012; Santos-Hernández, Miralles, Amigo, & Recio, 2018). Bovine milk proteins are a well-recognized source of bioactive peptides, with documented anti-hyperthensive, anti-thrombotic, opioid, anti-cancerogenic, immunostimulatory, antioxidant, antimicrobial as well as satiating properties (Corrochano, Buckin, Kelly, & Giblin, 2018; Sultan, Huma, Butt, Aleem, & Abbas, 2018). The average macronutrient composition of milk is 3.4% fat, 4.9% carbohydrate and 3.3% protein. The protein component of milk consists of 80% caseins (α_{s1}, α_{s2}, β and κ) and 20% whey (β-lactoglobulin (β-LG), α-lactalbumin (α-LA), bovine serum albumin (BSA), immunoglobulin (Ig) and lactoferrin (Lf)) (Ali, Lee, & Rutherfurd-Markwick, 2019). In animal and human studies, casein consumption generally leads to long-term satiety over 1–2 h, whereas whey has a short term satiety effect, observable within 20–30 min post consumption (Boirie et al., 1997; Hall, Millward, Long, & Morgan, 2003). This is likely related to the differences in rate of digestion in the upper gut (Dalziel, Young, McKenzie, Haggarty, & Roy, 2017). This review focuses on individual dairy-derived peptides and the evidence, or otherwise, of their influence on satiety pathways. Dairy protein hydrolysates and intact dairy proteins are also reviewed for their satiating properties. How their efficacy compares to other notable food derived peptides is also discussed. The review concludes with an overview on the mechanisms to protect bioactive peptides from the hydrolytic conditions of the gut. The ability of dairy peptides to influence body weight via lipid metabolism is not reviewed but has been reviewed previously (Ricci-Cabello, Olalla Herrera, & Artacho, 2012; Torres-Fuentes, Schellekens, Dinan, & Cryan, 2015).

2. Satiating bioactivity of caseins

2.1. Casein-derived peptides for satiety

Casein-derived peptides with satiety bioactivity demonstrated *in vitro*, *ex vivo* and/or *in vivo* are presented in Table 1. β-casein derivative β-casomorphin-7 (β-CM7, YPFPGPI) has attracted the most attention due to its association to A1/A2 milk controversy (Küllenberg de Gaudry et al., 2019), its opioid and antioxidant properties as well as its resistance to degradation upon GI digestion (Jahan-Mihan, Luhovyy, El Khoury, & Anderson, 2011). Osborne et al. (2014) demonstrated that β-CM7 (125–1000 μM) stimulated 2–2.4 fold higher secretion of CCK-8 from STC-1 enteroendocrine mouse cells compared to HBSS vehicle control ($P < 0.05$) (Osborne et al., 2014). However, no effect of β-CM7 on active GLP-1 secretion was observed for any of the tested concentrations over a 2 h incubation. Permeability studies of β-CM7 across Caco-2 monolayers indicate cleavage of this peptide by brush border membrane endopeptidases. Resulting peptide derivatives YP, GPI and FPGPI were found both in apical and basolateral solutions with FPGPI capable of stimulating secretion of CCK-8 from STC-1 cells ($P < 0.05$) (Osborne et al., 2014). β-CM7 may contribute to the satiety properties of fermented dairy foods, as its derivatives were identified in yogurt produced by *Streptococcus thermophilus* and *Lactobacillus delbrueckii* ssp. *bulgaricus* (Nguyen, Busetti, Johnson, & Solah, 2018). β-CM7 and its fragment β-CM4 were also identified *in vivo* in human jejunum after consumption of 30 g casein preload (Boutrou et al., 2013; Boutrou, Henry, & Sanchez-Rivera, 2015). A rat study indicated that modified β-casomorphins, at a dosage 179 mg/kg body weight, were effective in slowing gastric emptying in pups of either sex ($n = 10$, body mass 28 ± 3 g) (Daniel, Vohwinkel, & Rehner, 1990). This action was attributed to direct interaction of β-casomorphins with opioid receptors in the gut (Pupovac & Anderson, 2002). In another trial with Sprague-Dawley rats, β-CM7 stimulated production of somatostatin from mucosal tissues after 30 days of intra-gastric feeding at a dosage 7.5×10^{-7} mol/L compared to the saline control (Zong, Chen, Zhang, & Zou, 2007). Similarly, postprandial somatostatin plasma levels were increased after acute oral administration of 12 mg β-casomorphins to dogs (Schusdziarra et al., 1983). Effects of this somatostatin release on food intake were not studied in these trials, however involvement of somatostatin in satiety signaling via interaction with G protein-coupled somatostatin receptor subtype 2, inhibition of insulin and glucagon release, slowing of gastric acid secretion and inhibition of gastric motility was reported previously (Lucey, 1986).

Glycomacropeptide (GMP, 106–169 AA) (Table 1) is derived from κ-casein and is produced by the action of chymosin during cheese-making or indeed during gut transit (Daniel et al., 1990). Polymorphisms and levels of glycosylation of GMP influence its bioactivity, as GMP has 5 potential glycosylation sites available for carbohydrate chain attachment (Ricci-Cabello et al., 2012; Yvon, Beucher, Guilloteau, Le Huerou-Luron, & Corring, 1994). Effect of GMP and its carbohydrate-free form, caseinomacropeptide (CMP), on satiety biomarkers and food intake was demonstrated in cells, animals and humans (Luhovyy, Akhavan, & Anderson, 2007). Carbohydrate chains, their binding sites and the presence/absence of silaic acids were demonstrated to be important for the direct activation of luminal receptors, leading to secretion of CCK hormones (Yvon et al., 1994). Beucher, Levenez, Yvon, and Corring (1994) demonstrated that κ-casein post *in vitro* gastric digestion (187.5 mg/ml κ-casein), which presumably contained GMP, triggered a significant rise in CCK levels (both CCK-8 and CCK-33 were recognized by radioimmunoassay) when infused into isolated rat duodenojejunum (Beucher et al., 1994). Partially glycosylated GMP, released from κ-casein genetic variant A, was more effective at CCK stimulation, than unhydrolysed casein or GMP from κ-casein variant B or CMP (Beucher et al., 1994). At the same time glycosylation of CMP appears to slow its digestion by brush border membrane endopeptidases, which limits its bioaccessibility (Boutrou, Jardin, Blais, Tomé, & Léonil, 2008). In a human trial with 25 healthy subjects, a significant decrease in food intake *ad libitum* was observed for those receiving whey, compared to those who received whey without GMP (2877 ± 165 kJ vs. 3208 ± 178 kJ, $P < 0.05$) (Veldhorst et al., 2009). However, no effect of GMP was observed on postprandial plasma GLP-1 (active), ghrelin, insulin and individual satiety ratings by visual analogue scale (VAS) over the 120 min monitoring period. In a study with 10 women and 10 men, gender by preload interaction was found with satiety and energy compensation influenced more significantly in women after consumption of GMP preload, compared to men (Burton-Freeman, 2008). However, there is conflicting data with a 7 week feeding trial in 50 Wistar rats, showing no effect on body weight gain for those animals who received GMP-supplemented whey protein isolate (WPI) treatment, (100 g or 200 g GMP/kg), compared to those fed WPI alone (Royle, McIntosh, & Clifton, 2008). Interestingly, plasma insulin levels were lowered by GMP addition to the WPI diet. In a study with 20 overweight and obese men no effect on GLP-1, food intake or subjective

Table 1
Casein peptides with satiety bioactivity.

Peptide	Source/availability	Mechanism of action	Satiety effect		Reference
			Cell models/*ex vivo*	*In vivo*	
YPFPGP (β-CM7)	Cleaved from β-casein by the action of digestive enzymes	Stimulates CCK-8 secretion Stimulates somatostatin secretion Delays gut transit via interaction with gut opioid receptors	STC-1 cells Mucosal tissue of Sprague-Dawley rat –	– Dog Wistar rat	Osborne et al., 2014; Zong et al., 2007; Schusdziarra et al., 1983; Daniel et al., 1990; Pupovac & Anderson, 2002
FPGPI	Cleaved from β-CM7 by the action of digestive or brush border enzymes. Found in yogurt and human jejunum post casein consumption	Stimulates CCK-8 secretion	STC-1 cells	–	Osborne et al., 2014
Glycomacro-peptide (GMP) and caseinomacro-peptide (CMP)	Cleaved from κ-casein by the action of chymosin during cheese-making or *in vivo* digestion	Stimulates CCK hormones secretion Decreases *ad libitum* food intake Promotes growth of beneficial gut bacteria, which stimulate secretion of satiety hormones	Isolated duodenojejunum of rat – –	– Human BALB/c mice	Beucher et al., 1994; Veldhorst et al., 2009; Chen et al., 2012
GPVRGPFPIIV	Cleaved from β-casein in simulated digestion, pig digestion	Stimulates GLP-1 secretion	GLUTag cells	–	Komatsu et al., 2019
YIPIQYVLSR (casoxin C)	Cleaved from bovine κ -casein by the action of trypsin	Stimulates ileum contractions	Longitudinal muscle strip of guinea pig ileum	–	Yoshikawa & Chiba, 1992; Takahashi et al., 1998; Takahashi et al., 1997
YVPFPPF (casoxin D)	Cleaved from human α_{s1}-casein by the action of pepsin and chymotrypsin	Stimulates ileum contractions	Longitudinal muscle strip of guinea pig ileum	–	Yoshikawa & Chiba, 1992
RF	Encrypted in peptides, released by the action of chymosin on sodium caseinate	Stimulates CCK secretion Reduces food intake (I.p. injection) Delays gut transit (oral gavage)	STC-1 cells – –	– ddY mice ddY mice	Kagebayashi et al., 2012
LPQNIPPL	Cleaved from β-casein, found in the gouda-type cheese	Inhibits DPP-IV *in vitro*, lowers glucose in oral glucose tolerance test	–	Sprague-Dawley rat	Uenishi et al., 2012

appetite rating was observed after consumption of 50 g GMP compared to GMP-depleted whey (Clifton et al., 2009). Similarly in the work of Keogh et al. (2010) consumption of 41.3 g of minimally glycosylated GMP or 42.3 g of glycosylated GMP by 22 overweight or obese men resulted in similar levels of secreted CCK-8, *ad libitum* food intake and subjective appetite ratings (Keogh et al., 2010). In another work, Gustafson, McMahon, Morrey, and Nan (2001) reported that consumption of 0.4% and 2% CMP beverage did not alter *ad libitum* food intake and subjective appetite ratings in 47 healthy adults (Gustafson et al., 2001). Interestingly, GMP digestion with pepsin is documented to suppress appetite via regulation of gastric secretion, gastric emptying and CCK release (form not specified), whilst trypsin and chymotrypsin digestion leads to loss of bioactivity (Madureira, Tavares, Gomes, Pintado, & Malcata, 2010). Moreover, bovine GMP might have an indirect effect on satiety by promoting significant growth of beneficial gut bacteria. Such Chen et al. (2012) fed 6-week old mice with 0.1 mg/day GMP for 15 days and observed a 4.1 and 4.5-fold increase in *Bifidobacteria* and *Lactobacilli* respectively as a % of total fecal microbiota compared to the control group (Chen et al., 2012). Both these beneficial bacteria, *Bifidobacteria* (Vigsnæs, McConnell, & Salomonsson, 2017) and *Lactobacilli* (Belguesmia et al., 2016), can promote secretion of satiety hormones (GLP-1, PYY and CCK) up to 5-fold over 8 h incubation with STC-1 cells. However, long-term human studies are required to confirm satiety bioactivities of this widely produced dairy ingredient.

Simulated GI digestion of micellar casein concentrate but not sodium caseinate, revealed a β-casein peptide, GPVRGPFPIIV (199-209 AA) (Table 1), capable of dose-dependently stimulating GLP-1 release from the enteroendocrine cell line, GLUTag (Komatsu et al., 2019). A maximum effective dose of 5 mM was observed compared to buffer control (HEPES with 10 mM glucose). Interestingly, bioactivity of the crude digesta was more effective in stimulating GLP-1 release than the synthesized peptide, implying a synergistic effect with other bioactive peptides within micellar casein concentrate. Casein peptide tracking during skim milk powder digestion (*in vitro* dynamic and static models, pig digesta samples) indicates the appearance of GPVRGPFPIIV during the gastric phase and its rapid degradation during the duodenal phase (Egger et al., 2017).

Casoxin C (YIPIQYVLSR) (Table 1), derived from trypsin hydrolysate of bovine κ-casein, is known mostly for exhibiting opioid antagonism, however it also acts as an agonist of C3a receptors, resulting in ileum contractions (Yoshikawa & Chiba, 1992). This biphasic contraction was observed in longitudinal muscle strips of guinea pig ileum (Takahashi et al., 1998; Takahashi et al., 1997). This would be expected to suppress food intake (Ohinata & Yoshikawa, 2008), but to date casoxin C has not been tested in food intake studies. Its survival during gut transit is also unknown. Interesting, casoxin C naturally occurs in some semi-hard and ripening mold cheese varieties (Sienkiewicz-Szłapka et al., 2009). Another opioid antagonist casoxin D (YVPFPPF) (Table 1), derived from human α_{s1}-casein by the action of pepsin and chymotrypsin, has also demonstrated ileum-contracting bioactivity *ex vivo* (Yoshikawa & Chiba, 1992).

RF (Table 1) is a dipeptide that has been identified in several peptide sequences present in casein hydroylsate LFC25 (O'Halloran et al., 2018) and lies within the bitter taste α-casein peptide LRF (Lemieux & Simard, 1992). RF promotes secretion of CCK hormones from STC-1 via intracellular Ca^{2+} influx in a dose-dependent manner (0.3–3 mM) (Kagebayashi et al., 2012). Moreover, RF at a dosage of 10 mg/kg body weight significantly reduced cumulative food intake in male ddY mice 1–2 h post administrated via intraperitoneal (I.p.) injection. At a concentration of 100 mg/kg body weight, RF also significantly suppressed gut transit in ddY mice from 57% to 52% ($P < 0.05$) 30 min post oral gavage.

Partial and temporal inactivation of DPP-IV activity by food components could potentially prolong active GLP-1 circulation. More than 64 dairy peptides ranging in size from 2 to 14 AAs have been identified as DPP-IV inhibitors *in vitro* (Nielsen, Beverly, Qu, & Dallas, 2017). Interestingly, over 50% of them contain proline at the N-terminus, 22% are derived from β-casein, 13% - from κ-casein, 6% - from α_{s2}-casein and 5% - from α_{s1}-casein. Some of the DPP-IV inhibitory peptides, such as WR, WK and WL, naturally occur in milk protein hydrolysates (Nongonierma & FitzGerald, 2013). It is likely that some DPP-IV inhibiting peptides are also released from casein as it transits the hydrolytic conditions of the gut. For example, peptides LPVPQ (DPP-IV inhibition $IC_{50} = 43.8 \pm 8.8$ μM) and IPM (DPP-IV inhibition $IC_{50} = 69.5 \pm 8.7$ μM) were identified in human GI tract after milk ingestion (Nongonierma & FitzGerald, 2016). A derivative of κ-casein INNQFLPYPY was identified in the gastric digesta of premature infants (Nielsen, Beverly, Underwood, & Dallas, 2018). It is important to note that DPP-IV inhibition is usually demonstrated by enzymatic assays rather than observation in live cells or *in vivo* (Iwaniak, Darewicz, & Minkiewicz, 2018; Liu, Cheng, & Wu, 2019). DPP-IV inhibitory activity could result in lower post-prandial glucose *in vivo* (Lacroix & Li-Chan, 2016). For instance, a β-casein peptide, LPQNIPPL (Table 1), inhibiting DPP-IV with IC_{50} of 46 μM, measured by DPPIV-Glo™ Protease Assay Kit (Promega), was identified in a water-soluble extract of Gouda cheese (Uenishi, Kabuki, Seto, Serizawa, & Nakajima, 2012). Administration of 300 mg LPQNIPPL/kg body weight, to female Sprague-Dawley rats ($n = 6$) resulted in a significantly lower ($P < 0.02$) post-prandial glucose concentration over 120 min compared to the control group (20% glucose solution without peptide) during a glucose tolerance test. This glucose reduction was attributed to the DPP-IV inhibitory activity of the peptide (Uenishi et al., 2012). Finally, Murray et al. (2018), identified 11 peptides (12–56 AA in length) in β-casein hydrolysate fractions, with predicted or demonstrated insulin secretion modulation capabilities (Murray et al., 2018), but their ability to inhibit DPP-IV, influence satiety signaling or secretion of the incretin hormones GLP-1 or GIP was not investigated.

2.2. Casein hydrolysates for satiety

In many studies, individual peptide sequences have not been identified but rather evidence of satiety modulation is provided for casein hydrolystes (Table 2). Chaudhari et al. (2017) prepared casein hydrolysates by enzymatic digestion with pepsin and pancreatin and then proceeded to identify bioactive fractions (Chaudhari et al., 2017). Fraction F7 from a 1 kDa permeate of casein hydrolysate increased secretion of GLP-1 from STC-1 cells 2.5 fold and increased mRNA transcript levels of the *proglucagon* gene 5-fold ($P < 0.05$). The active mass peak of F7 fraction was determined by electrospray ionization-mass spectrometry to be 786 DA, indicating a 7–8 AA peptide, however the actual sequence remains unknown.

Schellekens et al. (2014) reported a 1 kDa permeate fraction of sodium caseinate hydrolysate, produced by pepsin digest, capable of acting as an agonist of the serotonin 5-HT_{2C} receptor (Table 2) (Schellekens et al., 2014). The serotonin pathway is a key modulator of food intake and is targeted by the pharma industry for appetite suppression (Coulter, Rebello, & Greenway, 2018). Human embryonic kidney (Hek293A) cells expressing the 5-HT_{2C} receptor increased calcium flux in response to this fraction, indicating activation of serotonin pathway (Schellekens et al., 2014). This 5-HT_{2C} receptor activation could not be explained by the presence of free tryptophan in the fraction. The 5-HT_{2A} and 5-HT_{2B} receptors remained unresponsive. C57BL/6 mice when I.p administrated with this sodium caseinate fraction, at a dose of 500 mg/kg body weight, significantly ($P < 0.01$) reduced their cumulative food intake compared to the vehicle control (HBSS with 20 mM HEPES) (Schellekens et al., 2014).

In our laboratory, 306 unique sodium caseinate hydrolysates were generated by enzymatic hydrolysis or bacterial fermentation (O'Halloran et al., 2018). These test samples were screened for their ability to release Ca^{2+} or increase intracellular cAMP in STC-1 cells. Increased levels of one or both of these biomarkers promote satiety hormone exocytosis (Gribble & Reimann, 2017). A chymosin

Table 2
Casein (proteins and hydrolysates) and satiety.

Component	Source/availability	Mechanism of action	Satiety effect		Reference
			Cell models/*ex vivo*	*In vivo*	
Fraction F7	Pepsin and pancreatin hydrolysate of casein, 1 kDa permeate	Stimulates GLP-1 secretion, increases *proglucagon* mRNA transcript levels	STC-1 cells	–	Chaudhari et al., 2017
Hydrolysate of sodium caseinate	Pepsin hydrolysate of sodium caseinate, 1 kDa permeate	Increases intracellular calcium influx (serotonin pathway) Reduces food intake (I.p. injection)	Hek293A cells expressing the 5-HT_{2C} receptor –	– C57Bl/6 mice	Schellekens et al., 2014
LFC25	Chimosin hydrolysate of sodium caseinate, 1 kDa permeate	Stimulates GLP-1 secretion Suppresses food intake (I.p. injection) No effect on food intake vs. unhydrolysed control (oral consumption)	STC-1 cells – –	– C57BL/6 mice C57BL/6 mice, crossbred pig; human	O'Halloran et al., 2018, Kondrashina et al., 2018, Le Roux et al., 2016
C2-WSE	Water-soluble extract of 4–10 months ripened cheese	Stimulates GLP-1 secretion No effect on food intake vs. reference cheese sample and saline (oral consumption)	STC-1 cells –	– C57BL/6 mice	Kondrashina et al., 2018
Casein digesta	Simulated gastric/intestinal digesta, *in vivo* jejunal digesta, tryptic casein hydrolysate	Stimulates CCK and GLP-1 release	STC-1 cells	–	Santos-Hernández et al., 2018
Intact casein	β-casein α-casein α-, β- and κ-caseins	Stimulates GLP-1 secretion Stimulates GLP-1 secretion Increase levels of *proglucagon* mRNA	STC-1 cells, NCI-H716 cells, STC-1 cells, NCI-H716 cells	– – –	Rafferty et al., 2011, Wazzan, 2018, Gillespie and Green, 2016, Wazzan, 2018
Intact casein	Sodium caseinate	Stimulates CCK secretion Stimulates GLP-1 secretion Stimulates GLP-1 and PYY secretion Increases plasma GLP-1 (oral consumption)	STC-1 cells STC-1 cells Ileal segments of porcine intestine – –	– – – Crossbred pigs Human	Geraedts et al., 2011, Kondrashina et al., 2018, Ripken et al., 2016, Kondrashina et al., 2018, Le Roux et al., 2016, Bohl et al., 2015

hydrolysate of sodium caseinate, LFC25, at 10 mg/ml (solids) significantly ($P < 0.05$) increased Ca^{2+} in STC-1 cells compared to its unhydrolysed control and buffer control (Krebs with 11 mM glucose). Correspondingly, this resulted in a 2-fold increase in secretion of total GLP-1 from STC-1 cells ($P < 0.05$) (O'Halloran et al., 2018). Free AAs in LFC25 were not responsible for its bioactivity. However, LFC25 did not increase mRNA transcript levels of *CCK* and significantly lowered mRNA transcript levels of *PYY* compared to unhydrolysed casein. In mice LFC25 at 750 mg/kg body weight suppressed cumulative food intake over 8 h after I.p. administration compared to Hanks control (O'Halloran et al., 2018), but did not have this effect after oral gavage compared to unhydrolysed sodium caseinate (Kondrashina, Bruen, et al., 2018). When administrated orally (15 g protein), no effect of LFC25 on food intake, postprandial levels of active GLP-1, glucose and insulin was observed in adult male pigs (Kondrashina, Bruen, et al., 2018; Kondrashina, Papkovsky, et al., 2018; Kondrashina, Seratlic, et al., 2018) or in humans (Le Roux, Engström, Björnfot, Fändriks, & Docherty, 2016) compared to unhydrolysed control. A < 1 kDa fraction of LFC25, containing only 4% protein, stimulated secretion of 296 pM GLP-1 from STC-1 cells, compared to 223 pM stimulated by LFC25 (75% protein) (O'Halloran et al., 2018). In this bioactive fraction, 17 of the most abundant peptides were identified, from which 88.2% were from α_{s1}-casein and 11.8% - from β-casein. Two of the abundant β-casein peptides (YQEPVLGPVRGPFPIIV and FLLYQEPVLGPVRGPFPIIV) contained sequence GPVRGPFPIIV (Table 1). If it is responsible for LFC25 bioactivity, then its degradation early in the duodenal phase (Egger et al., 2017) may explain the poor bioactivity of LFC25 in the gut. Simulated gastrointestinal digestion revealed that LFC25 lost 39% bioactivity during the gastric phase and 51% by the end of duodenal phase (Kondrashina, Bruen, et al., 2018; Kondrashina, Papkovsky, et al., 2018; Kondrashina, Seratlic, et al., 2018).

Cheese is made by the acidification of caseins, followed by casein proteolysis during ripening with bacterial peptidases. Screening of 10 water soluble extracts (WSEs) of Irish Cheddar cheese over a 10 month ripening period revealed GLP-1 stimulating bioactivity, using the STC-1 model, in 9 cheeses from 4 months ripening (Kondrashina, Seratlic, et al., 2018). The free AA components of these water soluble extracts were not positively correlated with GLP-1 bioactivity. One sample, C2-WSE, impressively increased GLP-1 secretion from STC-1 cells 37-fold at 8 months ripening compared to the vehicle control. However, when fed at 750 mg/kg body weight to mice, there was no significant decrease in cumulative food intake over a 7 h period compared to the reference cheese sample and saline controls, albeit food intake was reduced at a single time point (6 h) (Kondrashina, Seratlic, et al., 2018). Although post-prandial GLP-1 was not measured, this result infers that the hydrolytic conditions of the GI tract destroy GLP-1 secreting bioactivity of C2-WSE-8 M, outweighing the 62.9% increase in its DPP-IV inhibitory activity. These results were supported by data from *in vitro* GI digestion of C2-WSE-8 M with 68.6% and 99.9% loss of GLP-1 bioactivity by the end of gastric and intestinal phases respectively (Kondrashina, Seratlic, et al., 2018).

Egger and Ménard suggested that the protein degradation during gut transit could be as effective in releasing bioactive peptides from dairy proteins as targeted hydrolysis during processing (Egger & Ménard, 2017). Santos-Hernández (2018) observed that gastric digestion of casein stimulated active GLP-1 secretion, while intestinal digestion stimulated CCK hormones secretion from STC-1 cells (Santos-Hernández, Tomé, Gaudichon, & Recio, 2018). *In vivo* jejunal digestas of 3 subjects, who consumed a solution of 30 g of casein in 500 mL of water (i.e. 6% w/v), significantly ($P < 0.05$) stimulated release of CCK hormones and active GLP-1 from STC-1 cells. However, Geraedts, Troost, Fischer, Edens, and Saris (2011) maintained that casein hydrolysate was less effective in stimulation of CCK hormones or GLP-1 release from STC-1 cells compared to unhydrolysed casein (Geraedts et al., 2011).

It is important to note that casein hydrolysates and fractions are likely to contain free AAs. Several AAs individually (lysine, histidine, threonine, glutamic acid and methionine) and in combination are known to stimulate secretion of GLP-1 from enteroendocrine cells (Reimann, Williams, da Silva Xavier, Rutter, & Gribble, 2004; Reimer, 2006), but in several instances their role, if any, in hydrolysate bioactivity remains unknown. Bitterness of dairy protein hydrolysates is also likely to affect GI satiety response via taste receptors (Janssen et al., 2011), but the role of bitterness, or any aromatic compound, in satiety signaling is outside the remit of this review.

2.3. Native caseins for satiety

There is evidence that intact casein itself has satiating properties (Table 2). However, the physiological relevance of testing intact casein on enteroendocrine cell lines is questionable given that the GI tract will ensure casein is hydrolysed upon consumption. *In vitro,* intact casein at a concentration of 10 mg/ml applied directly to STC-1 cells resulted in a 5-fold increase in secretion of active GLP-1 over 4 h (Kondrashina, Papkovsky, & Giblin, 2018). No corresponding increase in mRNA transcript levels of *proglucagon* was observed indicating intact casein influenced GLP-1 exocytosis from intracellular stores rather than its production. Similarly, in the work of Rafferty et al. (2011), intact β-casein but not α-casein increased secretion of GLP-1 from STC-1 cells, while intracellular GLP-1 content remained unchanged (Rafferty et al., 2011). In the human NCI-H716 cell line, β-casein effectively stimulated GLP-1 secretion (3-fold increase) compared to the vehicle control (Wazzan, 2018). Surprisingly, in this enteroendocrine cell line *proglucagon* mRNA transcript levels were also significantly increased by α-, β- and κ-caseins. Such discrepancies between cell lines underscore the need to use a toolbox of satiety biomarkers and to test *in vivo* (Kuhre et al., 2016). In other work, intact α-casein was reported to be a superior GLP-1 stimulator compared to β- and κ-casein and this bioactivity survived hydrolysis with pepsin or trypsin over 90 min, but was destroyed by chymotrypsin (Gillespie & Green, 2016). Indeed, Geraedts et al. (2011) reported that simultaneous treatment of STC-1 cells with native or hydrolysed casein and trypsin for 30 min significantly improved secretion of CCK hormones but not GLP-1, compared to the treatment with casein/casein hydrolysate alone (Geraedts et al., 2011). In our work, levels of total GLP-1 secreted by STC-1 cells in response to sodium caseinate gradually increased over time during simulated gastrointestinal digestion, with a 150% increase in bioactivity after the gastric phase and 200% after duodenal digestion compared to time zero ($P < 0.01$) (Kondrashina, Bruen, et al., 2018). In fact, 15 min after arrival in the duodenal phase, sodium caseinate equaled LFC25 in its ability to secrete GLP-1 from STC-1 cells (Kondrashina, Bruen, et al., 2018) and increase post-prandial GLP-1 levels in 13 participants in a crossover study (15 g sodium caseinate or LFC25) (Le Roux et al., 2016). This study and the study by Egger et al., 2017 provides evidence that the hydrolytic conditions of the GI tract will convert intact casein into individual peptides, some of which are GLP-1 secretagogues.

Pipken et al. (2016) reported that 1% (w/v) intact casein (sodium caseinate, 82% purity) significantly ($P < 0.05$) stimulated release of GLP-1 and PYY from ileal segments of porcine intestines via release of serotonin from duodenum and ileum (Ripken et al., 2016). However, in an acute study with C57BL/6 mice ($n = 6$), intact β-casein at a dosage 500 mg/kg did not alter plasma GLP-1 and blood glucose levels, measured 30 min post oral gavage (Rafferty et al., 2011). Daily consumption of 60 g casein over 12 weeks by 13 healthy volunteers resulted in increases of postprandial GLP-1 by 878 pmol/L × 360 min ($P = 0.003$) compared to the consumption of whey (Bohl et al., 2015).

3. Satiating bioactivity of whey

3.1. Whey peptides for satiety

The bioactive properties of whey proteins have been recently

Table 3
Whey peptides with satiety bioactivity.

Peptide	Source/availability	Mechanism of action	Confirmed effect		Reference
			Cell models/*ex vivo*	*In vivo*	
ALPMH	Cleaved from β-LG by the action of pepsin and trypsin	Stimulates CCK secretion	STC-1 cells	–	Tulipano et al., 2017
LIVTQTMKG (lacto-ghrestatin)	Cleaved from β-LG by the action of thermolysin	Suppresses secretion of acylated ghrelin, decreases mRNA transcript levels of *preproghrelin* Decreases food intake and plasma ghrelin (oral consumption)	MGN3-1 cells –	– ddY mice	Aoki et al., 2017
LI	Dipeptide within LIVTQTMKG sequence	Suppresses secretion of acylated ghrelin	MGN3-1 cells	–	Aoki et al., 2017
HIRL (β-Lactotensin)	Cleaved from β-LG by the action of chymotrypsin	Stimulates ileum contractions, Delays gut transit, reduces food intake (I.p. injection, oral consumption)	Longitudinal muscle of guinea pig ileum –	– C57BL/6J mice	Pihlanto-Leppälä et. al, 1997; Hou et al., 2009
AFKAWAVAR (albutensin A)	Cleaved from serum albumin by the action of trypsin	Stimulates ileum contractions Delays gut transit, reduces food intake (I.p. injection)	Longitudinal muscle strip of guinea pig ileum –	– dYY mice	Yoshikawa & Chiba, 1992; Ohinata et al., 2002
Pyr-QRLGNQWAVGHLM-NH_2 (bombesin)	Bovine whey residue	Stimulates somatostatin secretion Reduces food intake, meal size, number of meals and body weight Stimulates CCK secretion and reduces appetite (infusion)	Perfused stomach of rat – –	– Diet-induced obese Sprague -Dawley rat Human	DuVal et al., 1981; Mhalhal et al., 2018 De Graaf et al., 2004
VAGTWY	Cleaved from β-LG by the action of trypsin	Inhibits DPP-IV (*in vitro*) Lowers plasma glucose level in oral glucose tolerance test	– –	– C57BL/6 mice	Uchida et al., 2011

reviewed (Dullius, Goettert, & de Souza, 2018). Table 3 lists the whey peptides with reported satiety bioactivity. Peptide ALPMH was identified in a β-LG hydrolysate, produced by pepsin and trypsin digestion, and has proven angiotensin-converting-enzyme inhibitory properties (Tulipano, Faggi, Cacciamali, & Caroli, 2017). At a concentration of 2 mM ALPMH increased secretion of CCK from STC-1 cells by 20 fold after a 12 h incubation compared to the DMEM (without serum) vehicle control ($P < 0.01$). To investigate whether the length of this peptide was important for its bioactivity, di- and tripeptides (LA, LL, LV, IPA and IPI) were synthesized and similarly assayed (Tulipano et al., 2017). None of these synthetic peptides stimulated significant increases in CCK (26–33) secretion at 2 mM concentration. Another dipeptide YL also present in β-LG, failed to stimulate secretion of active GLP-1 and CCK-8 from STC-1 cells at concentrations 0.125–1 mM (Osborne et al., 2014). Interestingly, synthesized scrambled sequence of ALPMH (PHLMA) increased CCK (26–33) secretion, suggesting that the length of peptide and the presence of certain AAs rather than the specific sequence were responsible for the observed bioactivity (Tulipano et al., 2017). It is important to note, that a 12 h incubation is not physiologically relevant for enterendocrine cells to interact with whey peptides, as whey has a digestibility indispensable AA score of 1.09 (Rutherfurd, 2015) and AAs can arrive in the blood stream as quickly as 30 min post whey ingestion (Luhovyy et al., 2007). At the same time, hydrolysates of β-LG and α-LA were 2–4 times more effective in stimulation of CCK (26–33) secretion from STC-1 cells compared to ALPMH peptide, suggesting bioactive synergies (Tulipano et al., 2017). In addition, effective concentrations of ALPMH (1–2 mM), could not be reached when β-LG underwent a simulated GI digestion (Tulipano et al., 2017), implying insufficient activity in the gut lumen post consumption of whey/β-LG. To generate large amounts of ALPMH a number of techniques, including microbial fermentation, enzymatic hydrolysis, chemical synthesis and recombinant DNA techniques have been explored by González-Ortega, López-Limón, Morales-Domínguez, and Soria-Guerra (2015) (González-Ortega et al., 2015).

Recently a ghrelin-secreting cell line mouse-grelinoma 3–1 (MGN3-1) was developed by Iwakura et al. (2010) which allows for screening peptides capable of suppressing ghrelin release (Iwakura et al., 2010). Aoki et al. (2017) identified lacto-ghrestatin, a 9 AA peptide LIVTQTMKG, produced by thermolyisin hydrolysis of β-LG, which lowered ghrelin secretion *in vitro* and *in vivo* (Aoki et al., 2017). LIVTQTMKG dose-dependently (10–100 μM) decreased secretion of acylated ghrelin from MGN3-1 cells over a 4 h incubation. Such regulation of ghrelin secretion is probably mediated via cAMP signaling, as cAMP levels in MGN3-1 cells treated with forskolin were decreased 2-fold when incubated with 100 μM LIVTQTMKG for 30 min. Moreover, mRNA transcript levels of *preproghrelin* and genes responsible for ghrelin activation were significantly reduced in MGN3-1 upon treatment with LIVTQTMKG. At a dosage of 1 mg/kg body weight this peptide decreased food intake over 4 h and plasma ghrelin levels 1 h post oral administration in fasted male ddY mice ($n = 17$), compared to the saline control. However, in non-fasted mice, basal ghrelin level was 4-fold lower and administration of LIVTQTMKG (1 g/kg body weight) had no effect within the same time period. A dipeptide of lacto-ghrestatin, LI, also suppressed ghrelin secretion from MGN3-1 cells, albeit less effectively, and was therefore not evaluated in mice (Aoki et al., 2017).

β-lactotensin (HIRL), derived from a chymosin digest of bovine β-LG , is known for its ileum contracting bioactivity, which was studied with longitudinal muscle of guinea pig ileum (Pihlanto-Leppälä, Paakkari, Rinta-Koski, & Antila, 1997). β-lactotensin shares homology to anorexigenic tridecapeptide neurotensin and acts as a neurotensin receptor agonist (Yoshikawa, 2015). Hou, Yoshikawa, and Ohinata (2009) I.p. injected β-lactotensin at the dosage of 100 mg/kg body weight and administrated β-lactotensin orally at the dosage 500 mg/kg body weight to fasted C57BL/6J mice and in both instances observed a significant decrease in food intake ($P < 0.05$). Surprisingly, the mechanism appeared not to involve the neurotensin receptor but rather the corticotrophin releasing factor (Hou et al., 2009).

Another ileum contracting peptide AFKAWAVAR named albutensin A was derived from serum albumin hydrolysed with trypsin (Yoshikawa & Chiba, 1992). It has an $IC_{50} = 3$ μM for contraction of guinea pig ileum muscle. Albutensin A delayed gastric emptying and decreased food intake in fasted dYY mice when I.p. administrated at the dose 0.3–1.0 μmol/mouse (Ohinata et al., 2002). It is believed that albutensin A acts via the C3a receptor (Ohinata et al., 2002), which plays a role in food intake regulation (Ohinata & Yoshikawa, 2008).

In 1984, Jahnke and Lazarus reported a bombesin-related peptide, with Mr of 3200, in bovine whey (Jahnke & Lazarus, 1984). Concentration of this peptide in whey can reach 1.2 ng/ml (Jahnke & Lazarus, 1984), which may be sufficient to interfere with endogenous gastrin releasing peptide (GRP) activity in the human gut. Recently it was demonstrated, that GRP and its homolog bombesin (Pyr-QRLGN-QWAVGHLM-NH2) act in the upper GI tract to reduce meal size and frequency (Washington, Aglan, & Sayegh, 2014). De Graaf et al. (2004) linked this endogenous peptide to appetite and food intake suppression via stimulation of CCK release (form is not specified) in animals and humans (De Graaf et al., 2004). Moreover, bombesin can increase levels of somatostatin secretion from perfused rat stomach (DuVal et al., 1981). Later studies demonstrated that GPR can inhibit gastric emptying and food intake by activation of GPCRs (Sayegh, 2013). A recent review draws attention to involvement of bombesin in stress-induced anorexia (Merali, Graitson, Mackay, & Kent, 2013). Interestingly, administration of bombesin with GLP-1 for 25 days via aorta infusion reduced food intake, meal size, number of meals and body weight in diet-induced obese Sprague Dawley rats more, than each peptide administrated separately (Mhalhal, Washington, Newman, Heath, & Sayegh, 2018). Whether milk borne GRP survives processing and gut transit to mediate an effect has not been ascertained.

There are a large number of peptides encrypted in whey proteins that act as DPP-IV inhibitors *in vitro* (Tulipano, Sibilia, Caroli, & Cocchi, 2011). For example, Silveira, Martínez-Maqueda, Recio, and Hernández-Ledesma (2013) identified peptide IPAVF from the trypsin digest of β-LG with remarkable DPP-IV inhibition activity *in vitro* ($IC_{50} = 44.7$ μM) (Silveira et al., 2013). From a database of milk bioactive peptides 25% of DPP-IV inhibitory peptides are derived from Lf, 17% from β-LG and 8% from α-LA. VAGTWY was identified from a trypsin digest of β-LG (Uchida, Ohshiba, & Mogami, 2011). This hexapeptide dose-dependently inhibited DPP-IV activity with IC_{50} of 174 μM, measured with Gly-Pro-p-nitroaniline substrate, while the crude β-LG hydrolysate has an $IC_{50} = 210$ μM. VAGTWY was able to significantly decrease postprandial blood glucose level over 120 min in glucose tolerance test, when orally administrated at a concentration of 300 mg/kg body weight to 10 fasted mice, compared to 0.01 M Tris-HCl buffer vehicle control. However post-prandial insulin was unaffected suggesting the glucose lowering observation may not be via DPP-IV inhibition or extension of GLP-1 half-life, but rather increased glucose uptake by hepatocytes (Tsuda, Iwasawa, Yokoyama, & Yamaguchi, 2017). Interestingly, DPP-IV inhibitory peptides IPAVFKIDA, IQKVAGTW and LKPTPEGDLE derived from β-LG were identified *in vivo* in the stomach of infants 2 h post consumption of mother's milk supplemented with infant formula (Nielsen et al., 2018).

3.2. Whey hydrolysates for satiety

Table 4 lists whey hydrolysates and proteins with satiety outputs *in vitro* and/or *in vivo*. Commercial whey hydrolysate DH32 (degree of hydrolysis 32%; 78.0% (w/w) protein, Carbery Ingredients) significantly stimulated secretion of insulin from BRIN BD11 β-cells and inhibited DPP-IV enzymatic activity ($IC_{50} = 1.5$ mg/ml) compared to the positive control (16.7 mM glucose and 10 mM Ala) and intact whey (Power-Grant et al., 2015). Another hydrolysate DH45 (degree of hydrolysis 45%; 84.0% (w/w) protein, Glanbia Nutritionals, Ireland) also demonstrated DPP-IV inhibitory properties ($IC_{50} = 1.1$ mg/ml)

Table 4
Whey (proteins and hydrolysates) and satiety.

Component	Source/availability	Mechanism of action	Satiety effect		Reference
			Cell models/ *ex vivo*	*In vivo*	
WPC hydrolysate, DH32	Optipep®, degree of hydrolysis 32% (78.0% (w/w) protein)	Inhibits DPP-IV (*in vitro*) Stimulates insulin secretion	– BRIN BD11 β-cells	– –	Power-Grant et al., 2015
Whey protein digesta	Simulated gastrointestinal digesta, *in vivo* jejunal digesta	Stimulates CCK and GLP-1 release	STC-1 cells	–	Santos-Hernández et al., 2018
Whey protein hydrolysate	Whey protein hydrolysed with pepsin, 1 kDa permeate	Increases calcium influx and activates the serotonin 5-HT_{2C} receptor No effect on food intake vs. HBSS with 20 nM HEPES (I.p. injection)	Hek293A cells expressing the 5-HT_{2C} receptor –	– C57BL/6 mice	Schellekens et al., 2014
Intact whey	WPC, WPI WPC	Increase levels of *proglucagon* mRNA Stimulates GLP-1 secretion	NCI-H716 STC-1 cells	– –	Wazzan, 2018 Power-Grant et al., 2015
Intact whey	α-LA, β-LG α-LA, Lf	Stimulate GLP-1 secretion Increased plasma concentration of PYY and *PYY* mRNA transcript levels in the colon, reduced food intake (oral consumption)	STC-1 cells –	– Diet-induced obese OP-CD rats	Gillespie et al., 2015, Zapata et al., 2018
Intact whey	WPI Liquid whey preload Liquid whey preload	Increases plasma CCK, decreases *ad libitum* energy intake and plasma ghrelinIncre ases plasma CCK, insulin, glucagon, GIP, and GLP-1, decreases plasma ghrelin, no effect on food intake vs. isocaloric mixed macronutrient preload Increases plasma GLP-1, PYY and satiety by VAS, lowers glucose levels, no effect on food intake vs. isocaloric maltodextrin preload	– – –	Overweight men Older men Obese women	Bowen et al., 2006, Giezenaar et al., 2018 Rigamonti et al., 2019

compared to unhydrolysed whey, but did not improve insulin secretion from BRIN BD11 β-cells. Neither of these hyrolysates could increase GLP-1 secretion from STC-1 cells above Krebs-1% BSA vehicle control, containing 1.8 g/l glucose (Power-Grant et al., 2015).

In contrast, simulated gastrointestinal digestas of whey protein promoted a dose-dependent (0.25–4 mg/ml) secretion of both GLP-1 and CCK hormones from STC-1 cells (5 and 10-fold respectively) compared to the vehicle control (Santos-Hernández et al., 2018). *In vivo* jejunal aspirates collected from 3 subjects, 1 h post consumption of a 30 g of a whey preload, as well significantly stimulated release of CCK hormones and GLP-1 from STC-1 cells (Santos-Hernández et al., 2018).

A 1 kDa permeate fraction of whey protein isolate digested with pepsin increased calcium influx and activated the serotonin 5-HT_{2C} receptor in transfected Hek cells (Schellekens et al., 2014). However, as distinct from its casein counter in Table 2, it was unable to suppress food intake in male C57BL/6 mice, when I.p. administrated at a dose 500 mg/kg body weight.

3.3. Intact whey proteins for satiety

Proglucagon mRNA transcript levels were increased significantly in NCI-H716 cells exposed to whey protein concentrate (WPC, 2-fold) and WPI (1.5-fold) (Wazzan, 2018). This resulted in a corresponding increase in total GLP-1 secretion. Previously our laboratory has shown that WPC significantly increased GLP-1 secretion from STC-1 cells (189.8 pM) compared to Krebs (81.4 pM) (Power-Grant et al., 2015). Gillespie, Calderwood, Hobson, and Green (2015) suggested that α-LA made the biggest contribution (Gillespie et al., 2015). β-LG also induced GLP-1 secretion but the result was confounded by its cell proliferation capacity (Gillespie et al., 2015). However, both groups reported loss of bioactivity once whey proteins were exposed to GI enzymes (Gillespie et al., 2015; Power-Grant et al., 2015). In agreement, GLP-1 secretagogue bioactivity of WPI, β-LG and α-LA was lost after simulated GI digestion with INFOGEST protocol whilst DPP-IV inhibition activity was increased 10-fold (Corrochano, Arranz, et al., 2018). Individual whey proteins (Lf and α-LA) constituting 15% of the diet (15 g protein), have been fed to diet-induced obese rats (n = 7–8) (Zapata, Singh, & Chelikani, 2018). Both whey proteins increased plasma concentrations of PYY and *PYY* mRNA transcript levels in the colon, and reduced food intake compared to the dairy-free control diet, with Lf being the most potent (Zapata et al., 2018).

Compared to casein, there is quite a considerable number of human studies investigating the effect of whey consumption on satiety biomarkers in the blood. Whether the satiety effect, if any, is a result of bioactive whey peptides release during gut transit or the release of AAs has yet to be determined. For example, Chungchunlam, Henare, Ganesh, and Moughan (2016) served 20 healthy women a preload enriched with 50 g of intact WPI or an AA mixture mimicking WPI (Chungchunlam et al., 2016). No difference was found in subjective hunger and food intake *ad libitum*, suggesting that the unique AA profile of whey is responsible for its satiating properties. In overweight men (n = 19), ghrelin levels were significantly lower 120 and 180 min post administration of WPI (55 g), compared to an isocaloric glucose preload (60 g) (Bowen, Noakes, Trenerry, & Clifton, 2006). In the same study *ad libitum* energy intake was significantly lower and CCK hormones secretion (over 180 min) was significantly higher after WPI consumption (4.279 MJ) compared to the consumption of glucose (4.772 MJ). Consumption of whey preload by healthy young men was shown to reduce postprandial glucose and insulin, but GIP levels over 230 min remained unaffected (Akhavan et al., 2014). In another study with 13 older men consumption of liquid preload with 70 g whey protein led to slowed gastric emptying, significantly lower ghrelin, higher GLP-1 and CCK compared to the mixed macronutrient preload of the same caloric value (280 kcal), however food intake was not lowered (Giezenaar et al., 2018). Similarly, in the work of Rigamonti et al. (2019), consumption of 45 g whey in a liquid preload by 9 obese women significantly increased plasma levels of GLP-1 and PYY, when postprandial glucose levels were significantly lower compared to isocaloric maltodextrin preload (Rigamonti et al., 2019). This result was supported by significantly higher satiety ratings of whey protein by visual analogue scale (VAS), however, *ad libitum* food intake was not lowered at 120 min compared to maltodextrin preload. The fact that increases in satiety hormone levels following protein consumption are not always correlated to decreases in food intake supports the evidence that there are other crucial parameters in food intake, such as sensory, social and cognitive factors (Kaelberer et al., 2018).

4. Efficacy of dairy-derived peptides/hydrolysates compared to other food-derived peptides and hydrolysates

To investigate the efficacy of dairy derived peptides/hydrolysates on satiety hormone secretion, we compared these bioactives in terms of molarity (peptides) or mg/ml powder (hydrolysates) to each other and to a number of peptides/hydrolysates form other food sources (pea, turmeric, beef, olive leaf and grape seed). Tulipano et al. (2017) revealed β-LG derivative ALPMH as the most potent of 9 peptides assayed for CCK stimulating potential in STC-1 cells (Tulipano et al., 2017). At a concentration of 1 mM it stimulated approximately 13-fold increase in secretion of CCK hormones (312 pg/ml) after 12 h incubation compared to the DMEM control. Other peptides studied in this system, β-CM7 (1 mM) and its derivative FPGPI (1 mM), resulted in 1.9- and 1.7-fold increase in CCK hormones over 3 h incubation respectively (Osborne et al., 2014). Pea hydrolysate B1 and B2 at concentration 1 mg/ml stimulated secretion of 515 and 586 pg/ml CCK hormones from STC-1 cells within 30 min, 3.12–3.55-fold increase, compared to 165 pg/ml with intact pea protein (Geraedts et al., 2011). The turmeric plant extract (50 mg/ml) resulted in 379 pg/ml CCK hormones and 347 pg/ml GLP-1 secretion from STC-1 cells within 60 min compared to 3.7 pg/ml and 8.6 pg/ml respectively by the short chain fatty acid control (102 and 40-fold increase) (Planes-Muñoz, López-Nicolás, González-Bermúdez, Ros-Berruezo, & Frontela-Saseta, 2018).

β-casein peptide GPVRGPFPIIV (5 mM) stimulated secretion of GLP-1 1.56-fold from GLUTag cells (from 825 to 1286 pg/ml) compared to buffer control (HEPES with 10 mM glucose) over 1 h incubation (Komatsu et al., 2019). However, beef hemoglobin peptide TKAVEH at a concentration 0.1 mM increased secretion of active GLP-1 20-fold (from 122 to 2549 pg/ml) in STC-1 cells compared to HEPES-Tris buffer control after a 2 h incubation (Caron et al., 2016). Other beef hemoglobin peptides with potent GLP-1 bioactivity, KAAVT, YGAE and ANVST, when added at 1 mM to STC-1 cells resulted in secretion of 4169, 4004 and 2911 pg/ml GLP-1 respectively (Caron et al., 2016). Olive leaf extract (1 mg/ml) increased secretion of GLP-1 from STC-1 cells 1.66-fold after 3 h incubation compared to buffer control (HEPES with 10 mM glucose) (Rafferty et al., 2011). Geraedts et al. (2011) reported an impressive 16-fold increase in GLP-1 secretion by 1 mg/ml B2 pea protein hydrolysate (45813 pg/ml) compared to HBSS control (Geraedts et al., 2011). Interestingly, this bioactivity appeared resistant to hydrolysis with trypsin.

Orally administrated hydrolysate of sodium caseinate, LFC25, failed to suppress food intake in mice (750 mg/kg body weight), pig (15 g protein contributed by LFC25, av. 429 mg/kg body weight) or in humans (15 g protein contributed by LFC25, av. 213 mg/kg body weight) compared to unhydrolysed casein (Kondrashina, Bruen, et al., 2018; Le Roux et al., 2016). LFC25 consumption, in pigs and humans, resulted in similar increases in post-prandial plasma GLP-1 to casein consumption which were in turn significant compared to the time zero. Oral gavage of C57BL/6 mice with 100 mg/kg body weight olive leaf extract together with glucose (18 mmol/kg) led to a significant increase (1.48 fold, $P < 0.05$) in post-prandial plasma GLP-1 levels 30 min post consumption, compared to the glucose only control (Rafferty et al., 2011). Grape-seed procyanidin extract (GSPE) administrated to Wistar rats at concentration 1 g/kg body mass stimulated 1.34-fold increase in

GLP-1 secretion and 1.32-fold increase in PYY from ileum and colon segments compared to the tap water control (Casanova-Martí et al., 2017). Moreover, consumption of GSPE at dosage 846 mg/kg body weight significantly decreased food intake in Wistar rats over 20 h compared to the tap water control (Serrano et al., 2017).

From a DPP-IV inhibition perspective, β-casein LPQNIPPL has an IC_{50} = 46 μM (Uenishi et al., 2012), whilst β-LG VAGTWY has an IC_{50} = 174 μM (Uchida et al., 2011) and the beef hemoglobin front runner, peptide VAAA, has IC_{50} = 141 μM (Caron et al., 2016) *in vitro*. Based on the data reviewed, plant-based ingredients both effectively stimulated satiety signaling *in vitro* and reduced food intake *in vivo* albeit unhydrolysed controls were often omitted. From a dairy perspective, β-casein peptides favorably compared to peptides/hydrolysates from other food sources as GLP-1 secretagogues and DPP-IV inhibitors with β-LG peptides targeting CCK hormones secretion. However, different enteroendocrine cell lines, the heterogeneity of enteroendocrine cell types, different incubation times, seeding density and different controls make direct comparison difficult. Moreover even for similar experimental designs, a variety of hormone immunoassays (RIA, ELISA, EIA), produced by different manufacturers with a range of specificity and cross-reactivity, have limited laboratory to laboratory comparisons.

5. Delivery systems for bioactive peptides

Orally administered proteins and peptides are generally broken down during GI digestion by proteolytic enzymes during the gastric or intestinal phase as well as by brush border membranes of the intestinal barrier. Hence only a small percentage of approved therapeutic peptides are orally delivered (Usmani et al., 2017). Pharmacological peptide solutions to appetite suppression include analogues of GLP-1 (liraglutide, exendin-4, semaglutide) (Lau et al., 2015; Marre et al., 2009; Sonne, Engstrøm, & Treiman, 2008) and structural variants of CCK (De Silva & Bloom, 2012; Pathak et al., 2018), administrated by injection rather than the oral route. These enzyme resistant forms of hormones can bind to corresponding receptors and stimulate satiety signaling, while their prolonged circulation results in stable effects on appetite (Nauck et al., 2006). Other peptides that are stable to enzymatic degradation include glycated CCK-8, (pGlu-Gln)-CCK-8, (pGlu-Gln)-CCK-8-PEG, CCK-7-PEG, CCK-9-PEG and CCK-10-PEG, which are shown to exhibit satiety effects (Pathak et al., 2018). Twice daily injection of 25 nmol/kg (pGlu-Gln)-CCK-8 to high-fat-fed mice decreased body weight by 25% and accumulated food intake by 19%, lowered non-fasting plasma glucose levels and significantly improved insulin sensitivity over 28 days study compared to the saline control (Irwin et al., 2012). The peptidic triagonst HXQGTFTSDKSKYLDERAAQDFVQWLL-DGGPSSGAPPS-NH2, which interacts with GLP-1, GIP and glucagon receptors, was tested in rat model of obesity (Finan et al., 2014). This triagonist reduced body weight of male HFD mice by 20%, cumulative food intake by 33% and significantly improved I.p. glucose tolerance after 10 days treatment with 3 nmol/kg dosage compared to the vehicle control. However, the daily injection regime and common side effects of nausea, constipation and diarrhea make hormone analogues unattractive for long term use (Astrup et al., 2012). As an alternative, increased circulation time of endogenous GLP-1 is achieved by administration of DPP-IV inhibitors, such as alogliptin, omarigliptin, sitagliptin, saxagliptin, etc., which are available in the oral form (Berger et al., 2018). Interestingly, such inhibitors are more effective in the treatment of diabetes than for weight management (Drucker & Nauck, 2006). However bearing in mind that DPP-IV has other peptidic substrates *in vivo*, prolonged inhibition of DPP-IV may lead to as yet unknown side effects (F. Gribble, 2008).

The most common approaches for protecting orally administered peptides (food derived or pharmacological) during gastric transit to the small or large intestine are protease inhibitors, structural modification of the peptide and encapsulating the peptide in a protective coating. However, protease inhibitors can interfere with the healthy GI digestion and nutrient absorption, whereas structural modification requires a specific system for each peptide to ensure the modifications do not interfere with the activity of the peptide, making these options less than ideal for food companies. The encapsulation of peptides is based on the protection and subsequent release from an encapsulation device with or without an additional coating, for targeted delivery to the small intestine or colon. The release mechanism can be triggered by changes in pH, time or digestion by intestinal bacteria. Due to the similar pH in the small and large intestine, precise pH-based release in the colon is hard to achieve. Colon targeted pH release systems normally begin releasing in the ileum of the small intestine (McConnell, Short, & Basit, 2008) whereas time-based systems rely on a continual release, which is normally controlled by adjusting the rate of swelling. The natural polymers chitosan (Yuan, Jacquier, & O'Riordan, 2018) and alginate (Xing, Dawei, Liping, & Rongqing, 2003) have been used in systems for the colonic delivery of insulin and bee venom peptide, respectively. In gels composed of cross-linked alginate and chitosan, the ratio of alginate to chitosan determined the rate of release of bovine serine albumin (Xu, Zhan, Fan, Wang, & Zheng, 2007). Time release systems for the colonic delivery of insulin have also been produced based on hydroxypropyl methylcellulose (HPMC) and polymethacrylate (Del Curto et al., 2014; Maroni et al., 2016). Protective coatings that are designed to be digested by intestinal bacteria are generally based on carbohydrate polymers such as chitosan, pectin and starch and its components such as amylose (Gough et al., 2018). Other encapsulating structures can be protein-based (Doherty et al., 2011; O'Neill, Egan, Jacquier, O'Sullivan, & O'Riordan, 2015), lipids including liposomes, solid/lipid nano particles, micro- and nano emulsions (McClements, 2018; Mohan, Rajendran, He, Bazinet, & Udenigwe, 2015) or self-assembled structures (Mosquera, Szyszko, Ho, & Nitschke, 2017). Polymers are normally used in conjunction with a binder such as ethyl cellulose or hydroxypropyl methylcellulose or a crosslinking agent such as glutaraldehyde (Shukla & Tiwari, 2012; Sinha & Kumria, 2001), all of which are acceptable for pharmaceutical application and food supplements. However, for including encapsulated bioactive peptides into food, it is necessary to limit the use of polymers to generally regarded as safe (GRAS) and food-grade materials, with a trend towards clean-label, kosher, halal or vegan composition and low processing history. An additional challenge is the cost and scale of encapsulation as food applications require the lowest possible cost and a reasonable scalability, both of which are still difficult to achieve. Current and future trends in encapsulation will include the protection of peptides within the food matrix itself such as in GI-stable emulsions as part of the natural or processed food matrix.

6. Concluding remarks

There is evidence that dairy protein consumption is satiating. To date, the majority of identified dairy peptides for satiety have been derived from either β-casein or β-LG. Several of those identified peptides have comparable bioactivities (GLP-1, CCK stimulation and DPP-IV inhibition) to peptides from other food sources. The advantage for dairy proteins is that they can be consumed in large quantities, as ingredients across a wide variety of food matrices. Such ingredients may decrease portion size and food intake over time. However surviving gut transit is a significant challenge. Indeed the solution maybe to harness the hydrolytic conditions of the gut to increase bioactive efficacy. With overweight and obesity affecting 12% of the world population (Fellinger et al., 2019), there are considerable commercial opportunities for scientifically-substantiated satiety-enhancing food peptides.

Ethics statement

Our research did not include any human subjects and animal experiments.

CRediT authorship contribution statement

Alina Kondrashina: Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **André Brodkorb:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing. **Linda Giblin:** Conceptualization, Investigation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial in-terests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Akhavan, T., Luhovyy, B. L., Panahi, S., Kubant, R., Brown, P. H., & Anderson, G. H. (2014). Mechanism of action of pre-meal consumption of whey protein on glycemic control in young adults. *The Journal of Nutritional Biochemistry, 25*(1), 36–43. https://doi.org/10.1016/j.jnutbio.2013.08.012.

Ali, A., Lee, S.-J., & Rutherfurd-Markwick, K. J. (2019). *Sports and Exercise Supplements Whey Proteins.* Elsevier579–635.

Amin, T., & Mercer, J. G. (2016). Hunger and satiety mechanisms and their potential exploitation in the regulation of food intake. *Current Obesity Reports, 5*(1), 106–112.

Aoki, H., Nakato, J., Mizushige, T., Iwakura, H., Sato, M., Suzuki, H., ... Ohinata, K. (2017). Lacto-ghrestatin, a novel bovine milk-derived peptide, suppresses ghrelin secretion. *FEBS letters*.

Astrup, A., Carraro, R., Finer, N., Harper, A., Kunesova, M., Lean, M., ... Rössner, S. (2012). Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *International Journal of Obesity, 36*(6), 843.

Baggio, L. L., & Drucker, D. J. (2007). Biology of incretins: GLP-1 and GIP. *Gastroenterology, 132*(6), 2131–2157.

Batterham, R. L., Cowley, M. A., Small, C. J., Herzog, H., Cohen, M. A., Dakin, C. L., ... Ghatei, M. A. (2002). Gut hormone PYY 3–36 physiologically inhibits food intake. *Nature, 418*(6898), 650.

Belguesmia, Y., Domenger, D., Caron, J., Dhulster, P., Ravallec, R., Drider, D., & Cudennec, B. (2016). Novel probiotic evidence of lactobacilli on immunomodulation and regulation of satiety hormones release in intestinal cells. *Journal of Functional Foods, 24*, 276–286. https://doi.org/10.1016/j.jff.2016.04.014.

Berger, J. P., SinhaRoy, R., Pocai, A., Kelly, T. M., Scapin, G., Gao, Y. D., ... Xu, S. S. (2018). A comparative study of the binding properties, dipeptidyl peptidase-4 (DPP-4) inhibitory activity and glucose-lowering efficacy of the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin in mice. *Endocrinology, Diabetes & Metabolism, 1*(1), e00002.

Beucher, S., Levenez, F., Yvon, M., & Corring, T. (1994). Effects of gastric digestive products from casein on CCK release by intestinal cells in rat. *Journal of Nutritional Biochemistry, 5*(12), 578–584.

Blundell, J. E., Dalton, M., & Gibbons, C. (2018). Food intake and appetite in the aetiology of obesity. *Advanced Nutrition and Dietetics in Obesity, 97*.

Bohl, M., Bjørnshave, A., Rasmussen, K. V., Schioldan, A. G., Amer, B., Larsen, M. K., ... O'Neill, S. (2015). Dairy proteins, dairy lipids, and postprandial lipemia in persons with abdominal obesity (DairyHealth): A 12-wk, randomized, parallel-controlled, double-blinded, diet intervention study. *The American Journal of Clinical Nutrition, 101*(4), 870–878.

Boirie, Y., Dangin, M., Gachon, P., Vasson, M.-P., Maubois, J.-L., & Beaufrère, B. (1997). Slow and fast dietary proteins differently modulate postprandial protein accretion. *Proceedings of the National Academy of Sciences, 94*(26), 14930–14935.

Boutrou, R., Gaudichon, C., Dupont, D., Jardin, J., Airinei, G., Marsset-Baglieri, A., ... Leonil, J. (2013). Sequential release of milk protein–derived bioactive peptides in the jejunum in healthy humans. *The American Journal of Clinical Nutrition, 97*(6), 1314–1323.

Boutrou, R., Jardin, J., Blais, A., Tomé, D., & Léonil, J. (2008). Glycosylations of κ-casein-derived caseinomacropeptide reduce its accessibility to endo-but not exointestinal brush border membrane peptidases. *Journal of Agricultural and Food Chemistry, 56*(17), 8166–8173.

Boutrou, R., Henry, G., & Sanchez-Rivera, L. (2015). On the trail of milk bioactive peptides in human and animal intestinal tracts during digestion: A review. *Dairy Science & Technology, 95*(6), 815–829.

Bowen, J., Noakes, M., Trenerry, C., & Clifton, P. M. (2006). Energy intake, ghrelin, and cholecystokinin after different carbohydrate and protein preloads in overweight men. *The Journal of Clinical Endocrinology & Metabolism, 91*(4), 1477–1483.

Burton-Freeman, B. M. (2008). Glycomacropeptide (GMP) is not critical to whey-induced satiety, but may have a unique role in energy intake regulation through cholecystokinin (CCK). *Physiology & Behavior, 93*(1), 379–387. https://doi.org/10.1016/j.physbeh.2007.09.010.

Caron, J., Cudennec, B., Domenger, D., Belguesmia, Y., Flahaut, C., Kouach, M., ... Ravallec, R. (2016). Simulated GI digestion of dietary protein: Release of new bioactive peptides involved in gut hormone secretion. *Food Research International, 89*, 382–390.

Casanova-Martí, À., Serrano, J., Blay, M. T., Terra, X., Ardévol, A., & Pinent, M. (2017). Acute selective bioactivity of grape seed proanthocyanidins on enteroendocrine secretions in the gastrointestinal tract. *Food & Nutrition Research, 61*(1), 1321347.

Chaudhari, D. D., Singh, R., Mallappa, R. H., Rokana, N., Kaushik, J. K., Bajaj, R., ... Grover, S. (2017). Evaluation of casein & whey protein hydrolysates as well as milk fermentates from Lactobacillus helveticus for expression of gut hormones. *The Indian Journal of Medical Research, 146*(3), 409.

Chaudhri, O., Small, C., & Bloom, S. (2006). Gastrointestinal hormones regulating appetite. *Philosophical Transactions of the Royal Society of London B: Biological Sciences, 361*(1471), 1187–1209.

Chen, Q., Cao, J., Jia, Y., Liu, X., Yan, Y., & Pang, G. (2012). Modulation of mice fecal microbiota by administration of casein glycomacropeptide. *Microbiology Research, 3*(1), 3.

Chungchunlam, S. M., Henare, S. J., Ganesh, S., & Moughan, P. J. (2016). Effect of whey protein and a free amino acid mixture simulating whey protein on measures of satiety in normal-weight women. *British Journal of Nutrition, 116*(9), 1666–1673.

Clifton, P. M., Keogh, J., Woonton, B., Taylor, C., Janakievski, F., & De Silva, K. (2009). Effect of glycomacropeptides (GMP) on satiety hormones and food intake. *Australian Journal of Dairy Technology, 64*(1), 29.

Corrochano, A. R., Arranz, E., De Noni, I., Stuknytė, M., Ferraretto, A., Kelly, P. M., ... Giblin, L. (2018). Intestinal health benefits of bovine whey proteins after simulated gastrointestinal digestion. *Journal of Functional Foods, 49*, 526–535.

Corrochano, A. R., Buckin, V., Kelly, P. M., & Giblin, L. (2018). Invited review: Whey proteins as antioxidants and promoters of cellular antioxidant pathways. *Journal of dairy science, 101*(6), 4747–4761.

Coulter, A. A., Rebello, C. J., & Greenway, F. L. (2018). Centrally acting agents for obesity: Past, present, and future. *Drugs, 78*(11), 1113–1132.

Cummings, D. E., & Overduin, J. (2007). Gastrointestinal regulation of food intake. *The Journal of clinical investigation, 117*(1), 13–23.

Dalziel, J., Young, W., McKenzie, C., Haggarty, N., & Roy, N. (2017). Gastric emptying and gastrointestinal transit compared among native and hydrolyzed whey and casein milk proteins in an aged rat model. *Nutrients, 9*(12), 1351.

Daniel, H., Vohwinkel, M., & Rehner, G. (1990). Effect of casein and β-casomorphins on gastrointestinal motility in rats. *The Journal of nutrition, 120*(3), 252–257.

De Graaf, C., Blom, W. A., Smeets, P. A., Stafleu, A., & Hendriks, H. F. (2004). Biomarkers of satiation and satiety. *The American Journal of Clinical Nutrition, 79*(6), 946–961.

De Silva, A., & Bloom, S. R. (2012). Gut hormones and appetite control: A focus on PYY and GLP-1 as therapeutic targets in obesity. *Gut and Liver, 6*(1), 10.

Del Curto, M. D., Palugan, L., Foppoli, A., Zema, L., Gazzaniga, A., & Maroni, A. (2014). Erodible time-dependent colon delivery systems with improved efficiency in delaying the onset of drug release. *Journal of Pharmaceutical Sciences, 103*(11), 3585–3593. https://doi.org/10.1002/jps.24150.

Doherty, S. B., Gee, V. L., Ross, R. P., Stanton, C., Fitzgerald, G. F., & Brodkorb, A. (2011). Development and characterisation of whey protein micro-beads as potential matrices for probiotic protection. *Food Hydrocolloids, 25*(6), 1604–1617. https://doi.org/10.1016/j.foodhyd.2010.12.012.

Dougkas, A., Reynolds, C. K., Givens, I. D., Elwood, P. C., & Minihane, A. M. (2011). Associations between dairy consumption and body weight: A review of the evidence and underlying mechanisms. *Nutrition Research Reviews, 24*(1), 72–95.

Drucker, D. J., & Nauck, M. A. (2006). The incretin system: Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *The Lancet, 368*(9548), 1696–1705.

Dullius, A., Goettert, M. I., & de Souza, C. F. V. (2018). Whey protein hydrolysates as a source of bioactive peptides for functional foods – Biotechnological facilitation of industrial scale-up. *Journal of Functional Foods, 42*, 58–74. https://doi.org/10.1016/j.jff.2017.12.063.

DuVal, J., Saffouri, B., Weir, G., Walsh, J., Arimura, A., & Makhlouf, G. (1981). Stimulation of gastrin and somatostatin secretion from the isolated rat stomach by bombesin. *American Journal of Physiology-Gastrointestinal and Liver Physiology, 241*(3), G242–G247.

Egger, L., & Ménard, O. (2017). Update on bioactive peptides after milk and cheese digestion. *Current Opinion in Food Science, 14*, 116–121.

Egger, L., Schlegel, P., Baumann, C., Stoffers, H., Guggisberg, D., Brügger, C., ... Portmann, R. (2017). Physiological comparability of the harmonized INFOGEST in vitro digestion method to in vivo pig digestion. *Food Research International, 102*, 567–574.

Feeney, E. L., O'Sullivan, A., Nugent, A. P., McNulty, B., Walton, J., Flynn, A., & Gibney, E. R. (2017). Patterns of dairy food intake, body composition and markers of metabolic health in Ireland: Results from the National Adult Nutrition Survey. *Nutrition & Amp Diabetes, 7*, e243. https://doi.org/10.1038/nutd.2016.54.

Fellinger, P., Fuchs, D., Wolf, P., Heinze, G., Luger, A., Krebs, M., & Winhofer, Y. (2019). Overweight and obesity in type 1 diabetes equal those of the general population. *Wiener klinische Wochenschrift, 131*(3–4), 55–60.

Finan, B., Yang, B., Ottaway, N., Smiley, D. L., Ma, T., Clemmensen, C., ... Tschöp, M. H. (2014). A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. *Nature Medicine, 21*, 27. https://doi.org/10.1038/nm.3761.

Geraedts, M. C., Troost, F. J., Fischer, M. A., Edens, L., & Saris, W. H. (2011). Direct induction of CCK and GLP-1 release from murine endocrine cells by intact dietary proteins. *Molecular Nutrition & Food Research, 55*(3), 476–484.

Giezenaar, C., Hutchison, A. T., Luscombe-Marsh, N. D., Chapman, I., Horowitz, M., & Soenen, S. (2018). Effect of age on blood glucose and plasma insulin, glucagon, ghrelin, CCK, GIP, and GLP-1 responses to whey protein ingestion. *Nutrients, 10*(1), 2.

Gillespie, A. L., Calderwood, D., Hobson, L., & Green, B. D. (2015). Whey proteins have

beneficial effects on intestinal enteroendocrine cells stimulating cell growth and increasing the production and secretion of incretin hormones. *Food Chemistry, 189*, 120–128.
Gillespie, A. L., & Green, B. D. (2016). The bioactive effects of casein proteins on enteroendocrine cell health, proliferation and incretin hormone secretion. *Food Chemistry, 211*, 148–159.
González-Ortega, O., López-Limón, A. R., Morales-Domínguez, J. F., & Soria-Guerra, R. E. (2015). Production and purification of recombinant hypocholesterolemic peptides. *Biotechnology Letters, 37*(1), 41–54.
Gough, R., Cabrera Rubio, R., O'Connor, P. M., Crispie, F., Brodkorb, A., Miao, S., ... Rea, M. C. (2018). Oral delivery of nisin in resistant starch based matrices alters the gut microbiota in mice. *Frontiers in Microbiology, 9*(1186), https://doi.org/10.3389/fmicb.2018.01186.
Gribble, F. (2008). RD Lawrence Lecture 2008 Targeting GLP-1 release as a potential strategy for the therapy of Type 2 diabetes. *Diabetic Medicine, 25*(8), 889–894.
Gribble, F. M., & Reimann, F. (2016). Enteroendocrine cells: Chemosensors in the intestinal epithelium. *Annual Review of Physiology, 78*, 277–299.
Gribble, F. M., & Reimann, F. (2017). Signalling in the gut endocrine axis. *Physiology & Behavior, 176*, 183–188.
Gustafson, D., McMahon, D. J., Morrey, J., & Nan, R. (2001). Appetite is not influenced by a unique milk peptide: Caseinomacropeptide (CMP). *Appetite, 36*(2), 157–163.
Hall, W., Millward, D., Long, S., & Morgan, L. (2003). Casein and whey exert different effects on plasma amino acid profiles, gastrointestinal hormone secretion and appetite. *British Journal of Nutrition, 89*(2), 239–248.
Holst, J. J. (2007). The physiology of glucagon-like peptide 1. *Physiological Reviews, 87*(4), 1409–1439.
Holst, J. J., & Deacon, C. F. (2005). Glucagon-like peptide-1 mediates the therapeutic actions of DPP-IV inhibitors. *Diabetologia, 48*(4), 612–615.
Hou, I.-C., Yoshikawa, M., & Ohinata, K. (2009). β-Lactotensin derived from bovine β-lactoglobulin suppresses food intake via the CRF system followed by the CGRP system in mice. *Peptides, 30*(12), 2228–2232.
Irwin, N., Frizelle, P., Montgomery, I. A., Moffett, R. C., O'Harte, F. P. M., & Flatt, P. (2012). Beneficial effects of the novel cholecystokinin agonist (pGlu-Gln)-CCK-8 in mouse models of obesity/diabetes. *Diabetologia, 55*(10), 2747–2758.
Iwakura, H., Li, Y., Ariyasu, H., Hosoda, H., Kanamoto, N., Bando, M., ... Akamizu, T. (2010). Establishment of a novel ghrelin-producing cell line. *Endocrinology, 151*(6), 2940–2945. https://doi.org/10.1210/en.2010-0090.
Iwaniak, A., Darewicz, M., & Minkiewicz, P. (2018). Peptides derived from foods as supportive diet components in the prevention of metabolic syndrome. *Comprehensive Reviews in Food Science and Food Safety*.
Jahan-Mihan, A., Luhovyy, B. L., El Khoury, D., & Anderson, G. H. (2011). Dietary proteins as determinants of metabolic and physiologic functions of the gastrointestinal tract. *Nutrients, 3*(5), 574–603.
Jahnke, G. D., & Lazarus, L. H. (1984). A bombesin immunoreactive peptide in milk. *Proceedings of the National Academy of Sciences, 81*(2), 578–582.
Janssen, S., Laermans, J., Verhulst, P.-J., Thijs, T., Tack, J., & Depoortere, I. (2011). Bitter taste receptors and α-gustducin regulate the secretion of ghrelin with functional effects on food intake and gastric emptying. *Proceedings of the National Academy of Sciences, 108*(5), 2094–2099.
Kaelberer, M. M., Buchanan, K. L., Klein, M. E., Barth, B. B., Montoya, M. M., Shen, X., & Bohórquez, D. V. (2018). A gut-brain neural circuit for nutrient sensory transduction. *Science, 361*(6408), eaat5236.
Kagebayashi, T., Kontani, N., Yamada, Y., Mizushige, T., Arai, T., Kino, K., & Ohinata, K. (2012). Novel CCK-dependent vasorelaxing dipeptide, A rg-P he, decreases blood pressure and food intake in rodents. *Molecular Nutrition & Food Research, 56*(9), 1456–1463.
Keogh, J. B., Woonton, B. W., Taylor, C. M., Janakievski, F., Desilva, K., & Clifton, P. M. (2010). Effect of glycomacropeptide fractions on cholecystokinin and food intake. *British Journal of Nutrition, 104*(2), 286–290.
Komatsu, Y., Wada, Y., Izumi, H., Shimizu, T., Takeda, Y., Hira, T., & Hara, H. (2019). Casein materials show different digestion patterns using an in vitro gastrointestinal model and different release of glucagon-like peptide-1 by enteroendocrine GLUTag cells. *Food chemistry, 277*, 423–431.
Kondrashina, A., Bruen, C., McGrath, B., Murray, B., McCarthy, T., Schellekens, H., ... McSweeney, P. L. (2018). Satiating effect of a sodium caseinate hydrolysate and its fate in the upper gastrointestinal tract. *Journal of Functional Foods, 49*, 306–313.
Kondrashina, A., Papkovsky, D., & Giblin, L. (2018). Physiological gut oxygenation alters GLP-1 secretion from the enteroendocrine cell line STC-1. *Molecular Nutrition & Food Research, 62*(3), 1700568.
Kondrashina, A., Seratlic, S., Kandil, D., Treguier, N., Kilcawley, K., Schellekens, H., ... Giblin, L. (2018). Irish Cheddar cheese increases glucagon-like peptide-1 secretion in vitro but bioactivity is lost during gut transit. *Food chemistry, 265*, 9–17.
Kuhre, R. E., Wewer, N. A., Deacon, C. F., Balk-Møller, E., Rehfeld, J. F., Reimann, F., ... Holst, J. J. (2016). Peptide production and secretion in GLUTag, NCI-H716, and STC-1 cells: A comparison to native L-cells. *Journal of Molecular Endocrinology, 56*(3), 201–211.
Küllenberg de Gaudry, D., Lohner, S., Schmucker, C., Kapp, P., Motschall, E., Hörrlein, S., ... Meerpohl, J. J. (2019). Milk A1 β-casein and health-related outcomes in humans: A systematic review. *Nutrition reviews, 77*(5), 278–306.
Lacroix, I. M., & Li-Chan, E. C. (2016). Food-derived dipeptidyl-peptidase IV inhibitors as a potential approach for glycemic regulation–Current knowledge and future research considerations. *Trends in Food Science & Technology, 54*, 1–16.
Lanou, A. J., & Barnard, N. D. (2008). Dairy and weight loss hypothesis: An evaluation of the clinical trials. *Nutrition reviews, 66*(5), 272–279.
Lau, J., Bloch, P., Schäffer, L., Pettersson, I., Spetzler, J., Kofoed, J., ... Steensgaard, D. B. (2015). Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *Journal of medicinal chemistry, 58*(18), 7370–7380.
Le Roux, C. W., Engström, M., Björnfot, N., Fändriks, L., & Docherty, N. G. (2016). Equivalent increases in circulating GLP-1 following jejunal delivery of intact and hydrolysed casein: Relevance to satiety induction following bariatric surgery. *Obesity Surgery, 26*(8), 1851–1858.
Lemieux, L., & Simard, R. (1992). Bitter flavour in dairy products. II. A review of bitter peptides from caseins: Their formation, isolation and identification, structure masking and inhibition. *Le Lait, 72*(4), 335–385.
Liu, R., Cheng, J., & Wu, H. (2019). Discovery of food-derived dipeptidyl peptidase IV inhibitory peptides: A review. *International Journal of Molecular Sciences, 20*(3), 463.
Luhovyy, B. L., Akhavan, T., & Anderson, G. H. (2007). Whey proteins in the regulation of food intake and satiety. *Journal of the American College of Nutrition, 26*(6), 704S–712S.
Lucey, M. R. (1986). Endogenous somatostatin and the gut. *Gut, 27*(4), 457.
Madureira, A., Tavares, T., Gomes, A. M. P., Pintado, M., & Malcata, F. X. (2010). Invited review: Physiological properties of bioactive peptides obtained from whey proteins. *Journal of Dairy Science, 93*(2), 437–455.
Maroni, A., Del Curto, M. D., Salmaso, S., Zema, L., Melocchi, A., Caliceti, P., & Gazzaniga, A. (2016). *In vitro* and *in vivo* evaluation of an oral multiple-unit formulation for colonic delivery of insulin. *European Journal of Pharmaceutics and Biopharmaceutics, 108*, 76–82. https://doi.org/10.1016/j.ejpb.2016.08.002.
Marre, M., Shaw, J., Brändle, M., Bebakar, W. W., Kamaruddin, N. A., Strand, J., ... Colagiuri, S. (2009). Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with type 2 diabetes (LEAD-1 SU). *Diabetic Medicine, 26*(3), 268–278.
McClements, D. J. (2018). Encapsulation, protection, and delivery of bioactive proteins and peptides using nanoparticle and microparticle systems: A review. *Advances in Colloid and Interface Science, 253*, 1–22.
McConnell, E. L., Short, M. D., & Basit, A. W. (2008). An *in vivo* comparison of intestinal pH and bacteria as physiological trigger mechanisms for colonic targeting in man. *Journal of Controlled Release, 130*(2), 154–160. https://doi.org/10.1016/j.jconrel.2008.05.022.
Merali, Z., Graitson, S., Mackay, J., & Kent, P. (2013). Stress and eating: A dual role for bombesin-like peptides. *Frontiers in Neuroscience, 7*(193), https://doi.org/10.3389/fnins.2013.00193.
Mhalhal, T. R., Washington, M. C., Newman, K. D., Heath, J. C., & Sayegh, A. I. (2018). Combined gastrin releasing peptide-29 and glucagon like peptide-1 reduce body weight more than each individual peptide in diet-induced obese male rats. *Neuropeptides, 67*, 71–78. https://doi.org/10.1016/j.npep.2017.11.009.
Mohan, A., Rajendran, S. R. C. K., He, Q. S., Bazinet, L., & Udenigwe, C. C. (2015). Encapsulation of food protein hydrolysates and peptides: A review. *RSC Advances, 5*(97), 79270–79278. https://doi.org/10.1039/C5RA13419F.
Morell, P., & Fiszman, S. (2017). Revisiting the role of protein-induced satiation and satiety. *Food Hydrocolloids, 68*, 199–210.
Mosquera, J., Szyszko, B., Ho, S. K. Y., & Nitschke, J. R. (2017). Sequence-selective encapsulation and protection of long peptides by a self-assembled FeII8L6 cubic cage. *Nature Communications, 8*, 14882. https://doi.org/10.1038/ncomms14882.
Murray, N. M., O'Riordan, D., Jacquier, J.-C., O'Sullivan, M., Holton, T. A., Wynne, K., ... Dallas, D. C. (2018). Peptidomic screening of bitter and nonbitter casein hydrolysate fractions for insulinogenic peptides. *Journal of dairy science, 101*(4), 2826–2837.
Nauck, M., Hompesch, M., Filipczak, R., Le, T., Zdravkovic, M., & Gumprecht, J. (2006). Five weeks of treatment with the GLP-1 analogue liraglutide improves glycaemic control and lowers body weight in subjects with type 2 diabetes. *Experimental and Clinical Endocrinology & Diabetes, 114*(08), 417–423.
Nguyen, D. D., Busetti, F., Johnson, S. K., & Solah, V. A. (2018). Degradation of β-casomorphins and identification of degradation products during yoghurt processing using liquid chromatography coupled with high resolution mass spectrometry. *Food Research International, 106*, 98–104.
Nielsen, S. D., Beverly, R. L., Qu, Y., & Dallas, D. C. (2017). Milk bioactive peptide database: A comprehensive database of milk protein-derived bioactive peptides and novel visualization. *Food Chemistry, 232*, 673–682.
Nielsen, S. D., Beverly, R. L., Underwood, M. A., & Dallas, D. C. (2018). Release of functional peptides from mother's milk and fortifier proteins in the premature infant stomach. *PloS one, 13*(11), e0208204.
Nongonierma, A. B., & FitzGerald, R. J. (2013). Inhibition of dipeptidyl peptidase IV (DPP-IV) by tryptophan containing dipeptides. *Food & Function, 4*(12), 1843–1849.
Nongonierma, A. B., & FitzGerald, R. J. (2016). Structure activity relationship modelling of milk protein-derived peptides with dipeptidyl peptidase IV (DPP-IV) inhibitory activity. *Peptides, 79*, 1–7. https://doi.org/10.1016/j.peptides.2016.03.005.
O'Halloran, F., Bruen, C., McGrath, B., Schellekens, H., Murray, B., Cryan, J. F., ... Giblin, L. (2018). A casein hydrolysate increases GLP-1 secretion and reduces food intake. *Food Chemistry, 252*, 303–310.
O'Neill, G. J., Egan, T., Jacquier, J. C., O'Sullivan, M., & O'Riordan, E. D. (2015). Kinetics of immobilisation and release of tryptophan, riboflavin and peptides from whey protein microbeads. *Food Chemistry, 180*, 150–155.
Ohinata, K., Inui, A., Asakawa, A., Wada, K., Wada, E., & Yoshikawa, M. (2002). Albutensin A and complement C3a decrease food intake in mice. *Peptides, 23*(1), 127–133.
Ohinata, K., & Yoshikawa, M. (2008). Food intake regulation by central complement system. In J. D. Lambris (Ed.). *Current Topics in Complement II* (pp. 33–44). New York, NY: Springer, US.
Olivos, D. R., McGrath, L. E., Turner, C. A., Montaubin, O., Mietlicki-Baase, E. G., & Hayes, M. R. (2014). Intraduodenal milk protein concentrate augments the glycemic and food intake suppressive effects of DPP-IV inhibition. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 306*(3), R157–R163. https://doi.org/10.1152/ajpregu.00358.2013.
Osborne, S., Chen, W., Addepalli, R., Colgrave, M., Singh, T., Tran, C., & Day, L. (2014). In vitro transport and satiety of a beta-lactoglobulin dipeptide and beta-casomorphin-7 and its metabolites. *Food & Function, 5*(11), 2706–2718.
Pathak, V., Flatt, P. R., & Irwin, N. (2018). Cholecystokinin (CCK) and related adjunct peptide therapies for the treatment of obesity and type 2 diabetes. *Peptides, 100*, 229–235.
Pihlanto-Leppälä, A., Paakkari, I., Rinta-Koski, M., & Antila, P. (1997). Bioactive peptide derived from in vitro proteolysis of bovine β-lactoglobulin and its effect on smooth

muscle. *Journal of Dairy Research, 64*(1), 149–155.
Planes-Muñoz, D., López-Nicolás, R., González-Bermúdez, C. A., Ros-Berruezo, G., & Frontela-Saseta, C. (2018). *In vitro* effect of green tea and turmeric extracts on GLP-1 and CCK secretion: The effect of gastrointestinal digestion. *Food & Function, 9*(10), 5245–5250. https://doi.org/10.1039/C8FO01334A.
Power-Grant, O., Bruen, C., Brennan, L., Giblin, L., Jakeman, P., & FitzGerald, R. J. (2015). *In vitro* bioactive properties of intact and enzymatically hydrolysed whey protein: Targeting the enteroinsular axis. *Food & Function, 6*(3), 972–980. https://doi.org/10.1039/C4FO00983E.
Pupovac, J., & Anderson, G. H. (2002). Dietary peptides induce satiety via cholecystokinin-A and peripheral opioid receptors in rats. *The Journal of Nutrition, 132*(9), 2775–2780.
Rafferty, E. P., Wylie, A. R., Elliott, C. T., Chevallier, O. P., Grieve, D. J., & Green, B. D. (2011). *In vitro* and *in vivo* effects of natural putative secretagogues of glucagon-like peptide-1 (GLP-1). *Scientia Pharmaceutica, 79*(3), 615–622.
Reimann, F., Williams, L., da Silva Xavier, G., Rutter, G., & Gribble, F. (2004). Glutamine potently stimulates glucagon-like peptide-1 secretion from GLUTag cells. *Diabetologia, 47*(9), 1592–1601.
Reimer, R. A. (2006). Meat hydrolysate and essential amino acid-induced glucagon-like peptide-1 secretion, in the human NCI-H716 enteroendocrine cell line, is regulated by extracellular signal-regulated kinase1/2 and p38 mitogen-activated protein kinases. *Journal of Endocrinology, 191*(1), 159–170.
Ricci-Cabello, I., Olalla Herrera, M., & Artacho, R. (2012). Possible role of milk-derived bioactive peptides in the treatment and prevention of metabolic syndrome. *Nutrition Reviews, 70*(4), 241–255.
Rigamonti, A. E., Leoncini, R., Casnici, C., Marelli, O., De Col, A., Tamini, S., ... Sartorio, A. (2019). Whey proteins reduce appetite, stimulate anorexigenic gastrointestinal peptides and improve glucometabolic homeostasis in young obese women. *Nutrients, 11*(2), 247.
Ripken, D., van der Wielen, N., Wortelboer, H. M., Meijerink, J., Witkamp, R. F., & Hendriks, H. F. (2016). Nutrient-induced glucagon like peptide-1 release is modulated by serotonin. *The Journal of Nutritional Biochemistry, 32*, 142–150.
Royle, P. J., McIntosh, G. H., & Clifton, P. M. (2008). Whey protein isolate and glycomacropeptide decrease weight gain and alter body composition in male Wistar rats. *British Journal of Nutrition, 100*(1), 88–93.
Rutherfurd, S. (2015). Protein digestibility-corrected amino acid scores and digestible indispensible protein quality in growing male rats. *Journal of Nutrition, 145*, 372–379.
Santos-Hernández, M., Miralles, B., Amigo, L., & Recio, I. (2018). Intestinal signaling of proteins and digestion-derived products relevant to satiety. *Journal of Agricultural and Food Chemistry, 66*(39), 10123–10131.
Santos-Hernández, M., Tomé, D., Gaudichon, C., & Recio, I. (2018). Stimulation of CCK and GLP-1 secretion and expression in STC-1 cells by human jejunal contents and in vitro gastrointestinal digests from casein and whey proteins. *Food & Function, 9*(9), 4702–4713. https://doi.org/10.1039/C8FO01059E.
Sayegh, A. I. (2013). The role of bombesin and bombesin-related peptides in the short-term control of food intake. *Progress in Molecular Biology and Translational Science, 114*, 343–370 Elsevier.
Sayon-Orea, C., Martínez-González, M. A., Ruiz-Canela, M., & Bes-Rastrollo, M. (2017). Associations between yogurt consumption and weight gain and risk of obesity and metabolic syndrome: A systematic review. *Advances in Nutrition, 8*(1), 146S–154S.
Schellekens, H., De Francesco, P. N., Kandil, D., Theeuwes, W. F., McCarthy, T., Van Oeffelen, W. E., ... Cryan, J. F. (2015). Ghrelin's orexigenic effect is modulated via a serotonin 2C receptor interaction. *ACS Chemical Neuroscience, 6*(7), 1186–1197.
Schellekens, H., Nongonierma, A. B., Clarke, G., van Oeffelen, W. E., FitzGerald, R. J., Dinan, T. G., & Cryan, J. F. (2014). Milk protein-derived peptides induce 5-HT2C-mediated satiety in vivo. *International Dairy Journal, 38*(1), 55–64.
Schusdziarra, V., Schick, A., Fuente, A. D. L., Specht, J., Klier, M., Brantl, V., & Pfeiffer, E. F. (1983). Effect of β-Casomorphins and analogs on insulin release in dogs. *Endocrinology, 112*(3), 885–889. https://doi.org/10.1210/endo-112-3-885.
Serrano, J., Casanova-Martí, À., Gual, A., Pérez-Vendrell, A. M., Blay, M. T., Terra, X., ... Pinent, M. (2017). A specific dose of grape seed-derived proanthocyanidins to inhibit body weight gain limits food intake and increases energy expenditure in rats. *European Journal of Nutrition, 56*(4), 1629–1636.
Shukla, R. K., & Tiwari, A. (2012). Carbohydrate polymers: Applications and recent advances in delivering drugs to the colon. *Carbohydrate Polymers, 88*(2), 399–416. https://doi.org/10.1016/j.carbpol.2011.12.021.
Sienkiewicz-Szłapka, E., Jarmołowska, B., Krawczuk, S., Kostyra, E., Kostyra, H., & Iwan, M. (2009). Contents of agonistic and antagonistic opioid peptides in different cheese varieties. *International Dairy Journal, 19*(4), 258–263.
Silveira, S. T., Martínez-Maqueda, D., Recio, I., & Hernández-Ledesma, B. (2013). Dipeptidyl peptidase-IV inhibitory peptides generated by tryptic hydrolysis of a whey protein concentrate rich in β-lactoglobulin. *Food Chemistry, 141*(2), 1072–1077.
Sinha, V. R., & Kumria, R. (2001). Polysaccharides in colon-specific drug delivery. *International Journal of Pharmaceutics, 224*(1–2), 19–38. https://doi.org/10.1016/S0378-5173(01)00720-7.
Sonne, D. P., Engstrøm, T., & Treiman, M. (2008). Protective effects of GLP-1 analogues exendin-4 and GLP-1 (9–36) amide against ischemia–reperfusion injury in rat heart. *Regulatory Peptides, 146*(1–3), 243–249.
Sultan, S., Huma, N., Butt, M. S., Aleem, M., & Abbas, M. (2018). Therapeutic potential of dairy bioactive peptides: A contemporary perspective. *Critical Reviews in Food Science and Nutrition, 58*(1), 105–115.
Takahashi, M., Moriguchi, S., Suganuma, H., Shiota, A., Tani, F., Usui, H., ... Yoshikawa, M. (1997). Identification of casoxin C, an ileum-contracting peptide derived from bovine κ-casein, as an agonist for C3a receptors. *Peptides, 18*(3), 329–336.
Takahashi, M., Moriguchia, S., Minami, T., Suganuma, H., Shiota, A., Takenaka, Y., ... Yoshikawa, M. (1998). Albutensin A, an ileum-contracting peptide derived from serum albumin, acts through both receptors for complements C3a and C5a. *Letters in Peptide Science, 5*(1), 29–35.
Tolhurst, G., Reimann, F., & Gribble, F. M. (2012). Intestinal sensing of nutrients. *Appetite Control,* 309–335 Springer.
Torres-Fuentes, C., Schellekens, H., Dinan, T. G., & Cryan, J. F. (2015). A natural solution for obesity: Bioactives for the prevention and treatment of weight gain. A review. *Nutritional neuroscience, 18*(2), 49–65.
Tsuda, Y., Iwasawa, K., Yokoyama, M., & Yamaguchi, M. (2017). Trypsin-treated β-Lactoglobulin improves glucose tolerance in C57BL/6 mice by enhancing AMPK activation and glucose uptake in hepatocytes. *Biological and Pharmaceutical Bulletin, 40*(11), 1917–1922.
Tulipano, G., Faggi, L., Cacciamali, A., & Caroli, A. M. (2017). Whey protein-derived peptide sensing by enteroendocrine cells compared with osteoblast-like cells: Role of peptide length and peptide composition, focussing on products of β-lactoglobulin hydrolysis. *International Dairy Journal, 72*, 55–62.
Tulipano, G., Sibilia, V., Caroli, A. M., & Cocchi, D. (2011). Whey proteins as source of dipeptidyl dipeptidase IV (dipeptidyl peptidase-4) inhibitors. *Peptides, 32*(4), 835–838.
Uchida, M., Ohshiba, Y., & Mogami, O. (2011). Novel dipeptidyl peptidase-4–inhibiting peptide derived from β-lactoglobulin. *Journal of Pharmacological Sciences, 117*(1), 63–66.
Uenishi, H., Kabuki, T., Seto, Y., Serizawa, A., & Nakajima, H. (2012). Isolation and identification of casein-derived dipeptidyl-peptidase 4 (DPP-4)-inhibitory peptide LPQNIPPL from gouda-type cheese and its effect on plasma glucose in rats. *International Dairy Journal, 22*(1), 24–30.
Usmani, S. S., Bedi, G., Samuel, J. S., Singh, S., Kalra, S., Kumar, P., ... Raghava, G. P. (2017). THPdb: Database of FDA-approved peptide and protein therapeutics. *PloS one, 12*(7), e0181748.
Veldhorst, M. A. B., Nieuwenhuizen, A. G., Hochstenbach-Waelen, A., Westerterp, K. R., Engelen, M. P. K. J., Brummer, R.-J. M., ... Westerterp-Plantenga, M. S. (2009). Effects of complete whey-protein breakfasts versus whey without GMP-breakfasts on energy intake and satiety. *Appetite, 52*(2), 388–395. https://doi.org/10.1016/j.appet.2008.11.014.
Vigsnæs, L. K., McConnell, B., & Salomonsson, E. (2017). *Synthetic composition for regulating satiety.* Google Patents.
Washington, M. C., Aglan, A. H., & Sayegh, A. I. (2014). The stomach and/or upper duodenum contain sites of action that control meal size and intermeal interval length by exogenous rat gastrin releasing peptide. *Peptides, 55*, 41–46. https://doi.org/10.1016/j.peptides.2014.02.004.
Wazzan, H. (2018). RMIT University. Regulation of glucagon-like peptide-1 (GLP-1) by milk protein fractions: An in vitro analysis.
Wei, Q., Krolewski, D. M., Moore, S., Kumar, V., Li, F., Martin, B., ... Watson, S. J. (2018). Uneven balance of power between hypothalamic peptidergic neurons in the control of feeding. *Proceedings of the National Academy of Sciences, 115*(40), E9489–E9498.
Worthington, J. J., Reimann, F., & Gribble, F. (2018). Enteroendocrine cells-sensory sentinels of the intestinal environment and orchestrators of mucosal immunity. *Mucosal Immunology, 11*(1), 3.
Xing, L., Dawei, C., Liping, X., & Rongqing, Z. (2003). Oral colon-specific drug delivery for bee venom peptide: development of a coated calcium alginate gel beads-entrapped liposome. *Journal of Controlled Release, 93*(3), 293–300.
Xu, Y. M., Zhan, C. Y., Fan, L. H., Wang, L., & Zheng, H. (2007). Preparation of dual crosslinked alginate-chitosan blend gel beads and in vitro controlled release in oral site-specific drug delivery system. *International Journal of Pharmaceutics, 336*(2), 329–337. https://doi.org/10.1016/j.ijpharm.2006.12.019.
Yoshikawa, M. (2015). Bioactive peptides derived from natural proteins with respect to diversity of their receptors and physiological effects. *Peptides, 72*, 208–225. https://doi.org/10.1016/j.peptides.2015.07.013.
Yoshikawa, M., & Chiba, H. (1992). *Biologically active peptides derived from food and blood proteins.* Amsterdam: Elsevier403–409.
Yuan, D. D., Jacquier, J. C., & O'Riordan, E. D. (2018). Entrapment of proteins and peptides in chitosan-polyphosphoric acid hydrogel beads: A new approach to achieve both high entrapment efficiency and controlled in vitro release. *Food Chemistry, 239*, 1200–1209. https://doi.org/10.1016/j.foodchem.2017.07.021.
Yvon, M., Beucher, S., Guilloteau, P., Le Huerou-Luron, I., & Corring, T. (1994). Effects of caseinomacropeptide (CMP) on digestion regulation. *Reproduction Nutrition Development, 34*(6), 527–537.
Zapata, R. C., Singh, A., & Chelikani, P. K. (2018). Peptide YY mediates the satiety effects of diets enriched with whey protein fractions in male rats. *The FASEB Journal, 32*(2), 850–861. https://doi.org/10.1096/fj.201700519RR.
Zong, Y.-F., Chen, W.-H., Zhang, Y.-S., & Zou, S.-X. (2007). Effects of intra-gastric beta-casomorphin-7 on somatostatin and gastrin gene expression in rat gastric mucosa. *World Journal of Gastroenterology: WJG, 13*(14), 2094.