REVIEW

Endocrine Cephalic Phase Responses to Food Cues: A Systematic Review

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ABSTRACT

Cephalic phase responses (CPRs) are conditioned anticipatory physiological responses to food cues. They occur before nutrient absorption and are hypothesized to be important for satiation and glucose homeostasis. Cephalic phase insulin responses (CPIRs) and pancreatic polypeptide responses (CPPPRs) are found consistently in animals, but human literature is inconclusive. We performed a systematic review of human studies to determine the magnitude and onset time of these CPRs. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to develop a search strategy. The terms included in the search strategy were cephalic or hormone response or endocrine response combined with insulin and pancreatic polypeptide (PP). The following databases were searched: Scopus (Elsevier), Science Direct, PubMed, Google Scholar, and The Cochrane Library. Initially, 582 original research articles were found, 50 were included for analysis. An insulin increase ($\geq$1 μIU/mL) was observed in 41% of the treatments (total $n = 119$). In 22% of all treatments the increase was significant from baseline. The median (IQR) insulin increase was 2.5 (1.6–4.5) μIU/mL, 30% above baseline at 5$\pm$ 3 min after food cue onset (based on study treatments that induced $\geq$1 μIU/mL insulin increase). A PP increase (>10 pg/mL) was found in 48% of the treatments (total $n = 42$). In 21% of the treatments, the increase was significant from baseline. The median (IQR) PP increase was 99 (26–156) pg/mL, 68% above baseline at 9$\pm$ 4 min after food cue onset (based on study treatments that induced $\geq$1 μIU/mL insulin increase). In conclusion, CPIRs are small compared with spontaneous fluctuations. Although CPPPRs are of a larger magnitude, both show substantial variation in magnitude and onset time. We found little evidence for CPIR or CPPPR affecting functional outcomes, that is, satiation and glucose homeostasis. Therefore, CPRs do not seem to be biologically meaningful in daily life. *Adv Nutr* 2020;11:1364–1383.

Keywords: human cephalic phase insulin response, human cephalic phase pancreatic polypeptide response, food intake control, glucose-homeostasis, Pavlovian responses, anticipatory responses, endocrinology, hormones, satiety

Introduction

Mechanisms that help to control food intake are important for maintaining a healthy weight (1–3). The regulation of food intake starts before the first bite, with the thought of food and visual and olfactory stimulation (4). During this anticipatory process cephalic phase responses (CPRs) are elicited. CPRs were first discovered by Pavlov (4–6), who originally named them "psychic secretions." The name later changed to CPRs since they are neurally mediated anticipatory and conditioned responses to food cues rather than responses to nutrients entering the digestive system (4–6).

CPRs are considered to be the first phase of digestion and include physiological responses to food-related cues such as the thought, smell, sight, and taste of food (7–9). CPRs described in the literature include increased salivation, bile secretion by the gallbladder, production of gastric juice, increased gut motility, and gastric and pancreatic endocrine secretions (5, 9–12). The latter include leptin, glucagon, insulin and pancreatic polypeptide (PP), and ghrelin secretion (8). Of these endocrine CPRs, insulin and PP release have been studied most often. Insulin is produced in the pancreatic β-cells and is involved in glucose homeostasis and food intake regulation (13, 14). The cephalic phase insulin response (CPIR) is thought to occur within 2–4 min after sensory stimulation and lasts for 8–10 min provided that no food is ingested (15–18). However, the magnitude of the

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Abbreviations used: CPIR, cephalic phase insulin response; CPPPR, cephalic phase pancreatic polypeptide response; CPR, cephalic phase response; iAUC, incremental AUC; MSF, modified sham feeding; PP, pancreatic polypeptide; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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CPIR is not well established and there are different definitions of what constitutes a CPIR (16, 17,19).

PP is an anorectic hormone synthesized by the F-cells in the pancreas, and is mainly released upon fat and protein ingestion. The cephalic phase pancreatic polypeptide response (CPPPR) is triggered through vagal activation and PP concentrations can increase up to 100% above baseline concentrations (15, 20). It is thought that cephalic PP concentrations remain elevated for ~30 min, if not followed by actual ingestion (15, 20).

The exact functions of the CPIR and CPPPR are not fully understood. However, based on literature reviews that we, and others, performed around a decade ago, we hypothesized that the CPIR and CPPPR (among other CPRs) are important for glucose homeostasis and the control of food intake (8, 21, 17). CPRs may activate short-term satiety signals that may help to reduce meal size. However, CPRs may also allow for larger meals as the responses prepare the body for incoming nutrients by starting digestive processes in anticipation of incoming nutrients (9, 22, 23). In line with that, CPR magnitude has been shown to correlate positively with motivation to eat, which may indirectly affect meal size and total daily energy intake (21). From an evolutionary perspective the ability to accommodate larger meals is an advantage but in the modern food environment it may promote overconsumption (24).

Besides the control of food intake, CPIRs may play an important role in glucose homeostasis. Work by Teff et al. showed that CPIRs can lead to a reduction in postprandial plasma glucose 16 min after food intake (25). Similarly, Ahren et al. found that blocking the neural pathways for CPRs through the use of trimethaphan resulted in higher postprandial plasma glucose concentrations (26).

CPIR and CPPPR have been found consistently in rodents (27–31). Simple sucrose solutions have shown to be sufficient to trigger CPIR in rodents (28, 31). However, in humans, studies have failed to observe a CPIR or CPPPR (4, 32–39). A wide range of food cues have been used to study CPIR and CPPPR in humans. Examples are: anticipating the consumption of favorite breakfast foods, modified sham feeding (MSF) of pizza, and ingestion of a mixed nutrient meal (40–42). The lack of a CPIR or CPPPR could, in part, be due to food cue specificity. It has been argued that multiple sensory modalities such as texture and flavor are needed to elicit a CPIR or CPPPR in humans (6, 43). For example, larger cephalic insulin increases have been observed when participants modified sham fed (chew and spat out) on apple pie compared with only swirling a sweet solution in their mouth (44).

Additionally, the lack of CPIRs and CPPPRs in some human studies might be due to the response being dependent on individual characteristics (45). For example, the response may be dependent of weight status, basal insulin concentrations, and eating behavior such as restrained eating or disordered eating (46–50). Studies also report cephalic phase insulin responders and nonresponders, but have not found a common divider among responders as yet (18, 32, 45, 51).

To summarize, endocrine CPRs are found consistently in animal (27–31), but not in human (4, 32–39) studies, which could be due to individual characteristics and specificity to certain food cues (45). In previous review articles the literature on human CPIR and CPPPR has been summarized and hypotheses have been posited on their roles in satiation and glucose homeostasis. However, the strength of evidence for these hypotheses has not been assessed quantitatively. Therefore, the main aim of the current review was to determine the magnitude and onset time of cephalic insulin and PP responses. In addition, their specificity for certain food cues and occurrences in specific population groups was explored. The secondary aim was to determine associations between CPIRs and CPPPRs and satiation and glucose homeostasis.

Methods

The study was preregistered with the International Prospective Register of Systematic Reviews (PROSPERO, http://www.prisma-statement.org/) before the start of the literature search (CRD42018100675). The Cochrane Collaboration's tool for assessing risk of bias was used to assess the quality of the studies included (52). Studies with a score below 5 were considered as having a "low risk" of bias and studies with a score above 5 were considered to have a "high risk" of bias. For descriptive purposes, additional quality parameters were included: whether or not the trial was (pre-) registered, whether a power calculation was done, whether dropouts or exclusion of participants was mentioned, whether there were compliance checks, and the presence and quality of a control group or control condition.

Search strategy

The search strategy was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (53). To obtain the final set of research articles the following 5 databases were searched: Scopus (Elsevier), Science Direct, PubMed, Google Scholar, and The Cochrane Library. The terms included in the search strategy were (cephalic*) or (hormone response) or (endocrine response) combined with insulin and PP. See **Supplementary Methods** for the detailed search strategy used in each database. An additional author and review search was performed for the most common authors occurring in the database. In the initial database we included only original research articles of human studies published in English between January 1945 and the search date (August 2018). The search was later updated in August 2019 but none of the new-found articles fulfilled the inclusion criteria. Review articles, commentaries, and case reports were not included.

All citations that came up in the different search databases were exported to the reference software EndNote™ X8.2. The titles and abstracts of the retrieved articles were screened by the first author (ML) to identify articles that potentially met the criteria as outlined below. To determine the reliability of the screening, Cohen's Kappa was calculated by having a second author (MM) screen 76 articles in duplicate. The

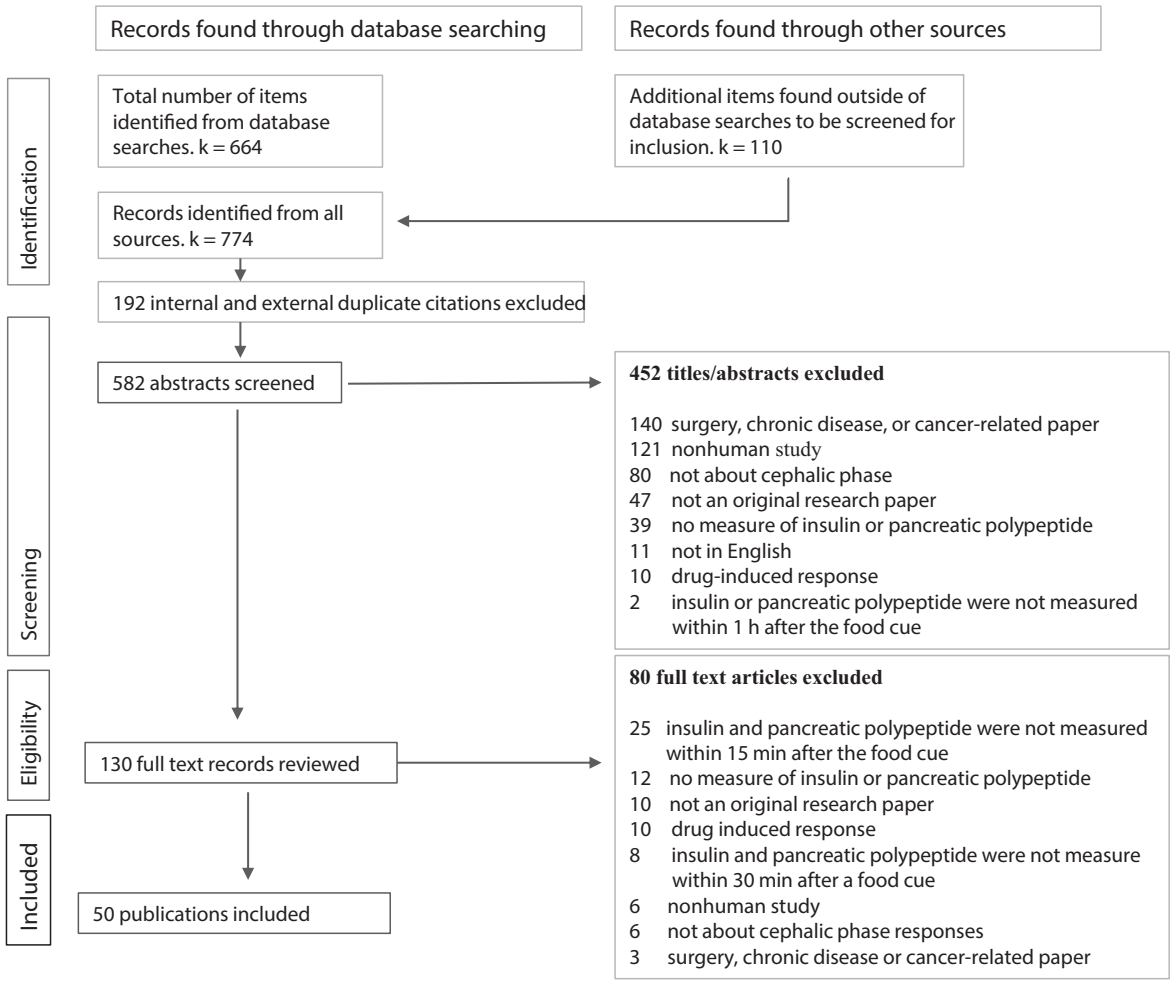

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the literature search to identify cephalic phase insulin and/or pancreatic polypeptide studies. Values are number of records or items (k) found at each stage of the literature search.

number of articles screened in duplicate is in line with the Cohen's Kappa method. The interrater reliability Cohen's Kappa score was 0.64 (substantial) (54, 55). The full texts of the potentially eligible studies were independently assessed for eligibility by 2 reviewers (authors ML and MM). Full texts that were rated differently were discussed by these reviewers until consensus was reached.

Inclusion and exclusion criteria

Studies were included if blood concentrations of insulin or PP were measured and when the intervention was food related, i.e., involved thought of food, anticipation of food consumption, or other sensory food cues such as sight, smell, and taste or actual food intake. Studies that included healthy participants (all weight classes) were included. To have a broader search range and because endocrine cephalic responses possibly play an important role in the (patho)physiology of diabetes and eating disorders, studies that included diabetic or eating disorder patient population groups were also included. Studies were excluded if they were related to other (chronic) diseases or surgery.

Cephalic phase endocrine responses are often described in the literature as a peak response occurring within the first 2–10 min after exposure to a food cue (44, 56–58). We used a 2-step approach to exclude articles that did not measure insulin and PP within this "cephalic" time frame. First, a quick screening was done by 2 reviewers (authors ML and MM) to include studies that measured insulin or PP within 30 min after the food cue. Second, the remaining articles were narrowed down to only those that reported insulin or PP concentrations or incremental AUC (iAUC) measures twice within 30 min after a food-related cue with 1 time point measured within the first 15 min. The second screening was done by 1 reviewer (author ML).

Article selection

An overview of the entire selection procedure [PRISMA flow diagram (53)] is shown in **Figure 1**. Using the search strategy as described in the 'search strategy' section, we identified

774 research articles. After removing duplicates this number was reduced to 582 unique research articles. These articles were screened based on their abstract and title to determine their eligibility. The main reasons for exclusion based on title/abstract were related to surgery or chronic diseases ($n = 140$) and nonhuman studies ($n = 121$). The full text of the remaining 130 articles was screened and the numbers of articles removed due to the following exclusion criteria were: PP and/or insulin was not measured twice within 30 min after a food-related intervention with 1 time point measured before the first 15 min ($n = 24$), $n = 8$ articles did not measure PP or insulin within the first 30 min, or measure PP and insulin at all ($n = 12$), $n = 10$ were nonoriginal research articles, $n = 10$ insulin or PP response was drug induced, $n = 6$ were nonhuman studies, $n = 6$ articles were not about cephalic phase, and $n = 3$ articles were about surgery, chronic diseases, or related to cancer. Finally, 50 articles were included for review and data extraction. Out of these, 3 articles described 2 experimental studies; thus, this review includes 53 studies.

Study characteristics and data extraction

Study characteristics such as the study design, (pre-) experimental conditions, participant characteristics, blood sample collection, and blood sample analysis were retrieved from the included articles. In addition, for each study, we extracted the insulin, glucose, and PP concentration for 5 different time points of a typical cephalic-(postprandial) curve, when applicable. These time points were baseline (where the time point closest to food cue onset was taken in case of multiple baselines), the first blood sample collected after a food cue, the first significant increase, the first peak or increase (which would depict a cephalic response), and the concentration of the second peak (postprandial increase). These time points were denoted per study and study condition. Besides the timing, the reported variability (SD, SE, 95% CI) of the peak was measured or derived from the article text. Data extraction from the figures was done with the use of a measurement tool included in Adobe Acrobat Reader DC (version 19). With this tool, the distance between 2 points can be measured with an accuracy of 0.1 mm.

As many studies only report the changes relative to baseline and not actual baseline concentrations, we calculated the absolute increase from baseline for each of the 5 time points per study condition. All concentrations were converted to the same unit (μIU/mL for insulin and pg/mL for PP) as follows: for insulin, values in pmol/L were divided by 6.0 to convert them to μIU/mL. Based on a molecular weight of 5807.57 Da, 1 IU insulin equals 0.0347 mg (59–61). For PP, values in pmol/L were divided by 0.239 to convert them to pg/mL based on a molecular weight of 4181.77 Da (60).

Summary of included studies, subpopulations, and treatments

See **Table 1** for an overview of all included studies and their findings. Of the 53 studies included, 9 studies measured both insulin and PP blood concentrations (plasma or serum), 37 measured only insulin, and 7 measured only pancreatic polypeptide. Combined, we found 46 studies that measured cephalic insulin responses and 16 that measured cephalic PP responses.

Subgroups were created to determine if CPIR and CPPPR are specific to certain population groups or food cue type, see **Supplementary Figure 1**. Study populations were classified based on the following subgroups: healthy normal weight (BMI 18–25 kg/m^2), healthy overweight/obese (BMI >25), diabetic (type I and II), and eating disorders (anorexia nervosa, bulimia nervosa, binge eating). Study conditions were classified as control (including fasting state and water) and treatments were grouped into food anticipation, rinsing of solutions/drinks, MSF, or actual food or drink intake.

Summary of methodologies used to study CPIR and CPPPR

Participant characteristics.

See Table 1 for an overview of all studies included. The average sample size per treatment was $n = 14.5$. Sample size ranged between $n = 4$ and $n = 64$. Out of the 53 included studies, 20 (38%) included both female and male participants, 20 (38%) included only males, and 12 (22%) only females. Over all studies included, the average age (mean ± SD) of the participants was 33.9±11.8 y with a range of 20.8–38.5 y.

(Pre-) experimental conditions.

The majority of the studies (37 out of 53, 70%) were performed in the morning (07:00–12:00) and the number of fasting hours ranged from 3–15 h. The majority of the studies had a 10–12 h or overnight fast ($n = 20$, 38%). Other common pretest conditions or instructions given to participants were: to eat a preload or standardized breakfast ∼4 h before the experiment and to refrain from exercise, alcohol, and smoking tobacco products 24 h before the study.

Blood sample collection and analysis.

The average acclimatization time between insertion of the cannula and the first blood sample was 39±49 min. Among the 53 included studies, 18 studies (34%) chose a 30-min acclimatization time and 16 studies (30%) did not report the acclimatization time. Studies included between 1 and 3 baseline samples and samples were drawn at 1–5 min intervals within the first 10–20 min after the food cue.

The majority of the studies collected blood plasma samples (63%) and most studies (61%) used RIA to determine the insulin concentration. Other common analysis methods used were electrochemiluminescence immunoassay and ELISA. The inter- and intra-assay CV was reported in 28% of the studies, 3 (7%) reported only the intra-assay CV, and 2 (4%) only the interassay CV.

To determine the PP concentrations, most studies (75%) collected plasma samples and 81% of the studies used RIA to determine the PP concentration. Nine of the 16 studies that measured CPPPRs (56%) reported both the inter- and intra-assay CV, and 1 reported only the interassay CV.

TABLE 1 Summary of studies investigating CPR to food cues of insulin and pancreatic polypeptide per participant group

Study	N, male/female	Age, y, mean ± SD or range	BMI, kg/m^2, mean ± SD or range	Population and food cue specifics	Exposure to food cue	Exposure duration	Conditions	Effect on		
								Glu	Ins	PP
Healthy normal-weight participants										
Lasschuijt, 2018 (32)	18M/0F	22 ± 2	22 ± 2	Strawberry gel model foods	MSF	15 min	Hard vs. soft and low vs. high sweet model foods	=	=	=
Kashima, 2017 (62)	3M/5F	21 ± 2	20.4 ± 2.1	15% glucose solution load	Intake	30 seconds max.	With and without sweet taste perception	⇨*	⇨*	n.a.
Morey, 2016 (19)	10M/0F	37.8 ± 3.4	18.5–30	Oral vs. gastric infusion of 400 mL tomato cream soup	Intake	Freely	Oral	⇨	⇧⇧	n.a.
							Gastric	⇨	⇨	n.a.
Cedernaes, 2016 (33)	16M/0F	22.9 ± 0.7	22.9 ± 0.5	With and without normal sleep duration evening before. Sucrose solution	Rinse	45 sec	Little sleep (4.25 h)	=	=	n.a.
							Good sleep (8 h)	=	=	n.a.
Mennella, 2015 (63)	10M/0F	28 ± 1	22.7 ± 0.6	Milk pudding no taste (control), sweet (liked), bitter (unliked)	MSF	3 min	Bitter pudding	n.s.	=	=
							Sweet pudding	n.s.	⇧	⇧*
							Control (tasteless control pudding)	n.s.	⇧	=
Veedfald, 2015 (64)	25M/0F	67.1 ± 1	25 ± 1	Glucose load	Intake	15 min	Intake glucose load	⇨	n.a.	⇨
Zhu, 2014 (65)	10M/0F	27 ± n.s.	23.4 ± 0.9	Normal to overweight participants. MSF on different macronutrient food items	MSF	3 min	Macadamia nuts	⇨*	=	n.a.
							Mozzarella cheese	⇨*	=	n.a.
							Kellogg frosted cereal	⇨*	⇧*	n.a.
							Water	⇨*	=	n.a.
Spetter, 2014 (66)	14M/0F	24.6 ± 3.8	22.3 ± 1.6	Gastric load (water), gastric load (chocolate milk), oral load (chocolate milk)	Gastric vs. oral intake	n.s.	Oral caloric	⇨	⇨	n.a.
							Gastric caloric	⇨	⇨	n.a.
							Gastric noncaloric	⇨	=	n.a.
Dušková, 2013 (67)	15M/0F	28.8 ± 6.3	23.4 ± 1.7	Sucrose, sweetener and water rinse	Rinse	n.s.	Sucrose	=	⇧*	n.a.
							Aspartame	=	⇧	n.a.
							Water	=	=	n.a.
Ford, 2011 (34)	1M/7F	22–27	18.8–23.9	Load followed by rinse same solution. Control: 50 mL water preload with rinse sucralose	Intake+ rinse	MSF 1 min per swallow	Water	=	=	n.a.
							Cephalic sucralose	=	=	n.a.
							Sucralose	=	=	n.a.
							Maltodextrin + sucralose	⇨	⇨	n.a.

(*Continued*)

TABLE 1 (*Continued*)

Study	N, male/female	Age, y, mean ± SD or range	BMI, kg/m^2, mean ± SD or range	Population and food cue specifics	Exposure to food cue	Exposure duration	Conditions	Effect on		
								Glu	Ins	PP
Lindgren, 2011 (35)	12M/0F	23.2 ± 2.2	21.9 ± 2	Oral ingestion of 3 mL/kg lipid emulsion	Intake	n.s.	Oral exposure to fat	⇨	⇨	n.a.
Bello, 2010 (48)	0M/22F	24.8 ± 6.5	23.1 ± 2.7	Yogurt different fat% with added fat free cocoa	MSF	3 min	Nonfat placebo, fat placebo, fat Naltrexone	=	=	n.a.
Massolt, 2010 (36)	0M/12F	26.6 ± n.s.	18–25	Eating and smelling 30 g of dark chocolate	Smell, intake	5 min max	Control (fasted)	=	=	n.a.
							Smell	=	=	n.a.
							Eat	=	⇨	n.a.
Just, 2008 final study (56)	11M/8F	26 ± 5	23.3 ± 2.3	Normal to overweight participants. 10 mL sweet taste solution	Rinse	45 sec	Sucrose	=	⇧*	n.a.
							Saccharin	=	⇧*	n.a.
Just, 2008 pilot study (56)	2M/3F	29 ± 7.6	n.s.	Normal to overweight participants, 10 mL of different taste solutions	Rinse	45 seconds	Starch	=	⇧	n.a.
							QHCL (bitter)	=	⇧	n.a.
							Citric acid (sour)	=	=	n.a.
							MSG (umami)	=	=	n.a.
							NaCl (salty)	=	=	n.a.
							Distilled water	=	⇧	n.a.
Crystal, 2006 (47)	0M/22F	18–29	22.4 ± 0.9	MSF high-fat and nonfat cake and fasted control	MSF	3 min	High-fat cake	=	=	⇧*
							Nonfat cake	=	=	⇧
							Control (fasted)	=	=	=
Smeets, 2005 (68)	5M/0F	20.4 ± 2.5	21.7 ± 1.1	(Sweet) water solutions	Intake	n.s.	Water	=	=	n.a.
							Water + 75 g glucose	⇨	⇧⇧	n.a.
							Water + aspartame	=	=	n.a.
							Water + maltodextrin	⇨	⇧⇧	n.a.
Hoentjen, 2001 (15)	3M/5F	19–24	n.s.	Bread, cheese, hamburger, 20 g margarine, 1 boiled egg, and 150 mL tea	Saline infusion and MSF	30 min	Mixed nutrient meal	n.a.	n.a.	⇧⇧
Robertson, 2001 (69)	4M/6F	35.5 ± n.s.	24.1 ± n.s.	Cheese pizza served with a glass of full fat milk and cream	MSF and intake	10–15 min	Water	=	=	=
							MSF	⇨	⇧	⇧
							Meal intake	⇨	⇨	⇧⇧

(*Continued*)

TABLE 1 (*Continued*)

Study	N, male/female	Age, y, mean ± SD or range	BMI, kg/m^2, mean ± SD or range	Population and food cue specifics	Exposure to food cue	Exposure duration	Conditions	Effect on		
								Glu	Ins	PP
Ahren, 2001 (26)	0M/12F	63 ± n.s.	27.7 ± n.s.	Breakfast bread, margarine, marmalade, cheese (15% fat), cup of coffee	Saline infusion and intake	5 min max	Experiment 1	⇨*	⇧*	⇧⇧
							Experiment 2	⇨*	⇧*	n.a.
Morricone, 2000 (37) study 1	4M/8F	39.9 ± 4.4	22.5 ± 3.9	20 mg/10 mL saccharin/water solution and 5 mL lemon juice in 10 mL water. Control: water	Rinse	2 min	Saccharin, lemon, water	=	=	n.a.
LeBlanc, 1998 (70)	5M/3F	51 ± 6	24.9 ± 1.7	250 g steak	Intake	Freely	Intake of steak	=	⇧⇧*	n.a.
Abdallah, 1997 (71)	12M/0F	18–27	20–24	Sweet tablets with sucrose, aspartame or polydextrose	Suck on tablet	5 min	Sucrose	⇨	⇨	n.a.
							Aspartame	=	=	n.a.
							Polydextrose	=	=	n.a.
Teff, 1996 (72)	0M/13F	19–27	18–24	Palatable and unpalatable food items (based on preference of participant)	MSF	2 min	Palatable	=	⇧	n.a.
							Unpalatable	=	⇧	n.a.
Teff, 1996 (25)	8M/0F	25.5 ± 9.5	23.0 ± 2.9	Intragastric infusion of glucose with or without MSF peanut butter sandwich	MSF	5 min	MSF	⇨	⇧⇧	n.a.
							No MSF	⇨	⇧⇧	n.a.
Yegen, 1995 (73)	15M/0F	19–31	n.s.	Saline infusion MSF mixed meal; steak, French fried potatoes, salad, bread	MSF	40 min	MSF mixed nutrient meal	n.a.	n.a.	⇧*
Secchi, 1995 (40)	$N = 5$	25–35	n.s.	Intake of pizza	Intake	5–10 min	Intake of pizza	=	⇧	n.a.
Glasbrenner, 1995 (74)	14M/10F	43 ± n.s.	n.s.	Preparation of a sandwich and MSF a sandwich with butter, bacon, and 2 scrambled eggs	Visual & smell, intake	10 min visual, 20 min MSF	Visual	n.s.	n.a.	=
							MSF	n.s.	n.a.	⇧
Teff, 1995 (44) study1	15M/0F	25 ± 6	22.8 ± 1.5	Exposure to sweet solutions and apple pie	Rinse or MSF	1 min	Water	=	=	n.a.
							Aspartame	=	=	n.a.
							Saccharin	=	=	n.a.
							Sucrose	=	=	n.a.
							Apple pie	=	⇧*	n.a.

(*Continued*)

TABLE 1 (*Continued*)

Study	N, male/female	Age, y, mean ± SD or range	BMI, kg/m^2, mean ± SD or range	Population and food cue specifics	Exposure to food cue	Exposure duration	Conditions	Effect on		
								Glu	Ins	PP
Teff, 1995 (44) study2	16M/0F	26 ± 5	23.3 ± 1.6	Exposure to sweet solutions and apple pie	Rinse or MSF	3 min	Water	=	=	n.a.
							Aspartame	=	=	n.a.
							Saccharin	=	=	n.a.
							Sucrose	=	=	n.a.
							Apple pie	=	⇧*	n.a.
Lieverse, 1994 (49)	3M/12F	35 ± 2.5	21.2 ± 0.4	Mixed nutrient meal; hamburger, bread, mayonnaise	Intake	30 min	Intake mixed nutrient meal	⇨	n.a.	⇧⇧
Johnson, 1994 (38)	0M/8F	26.6 ± n.s.	19.5 ± n.s.	Mental imagery and viewing cookies and milk	Thinking of and viewing	2/2 min	Thought and view of cookies and milk	=	=	n.a.
Witteman, 1994 (75)	4M/3F	48 ± n.s.	n.s.	Codfish (protein), walnut (fat), banana (CHO), fat solution	MSF	30 min	Codfish	n.a.	n.a.	⇧
							Walnut	n.a.	n.a.	⇧
							Banana	n.a.	n.a.	=
							Fat solution	n.a.	n.a.	⇧
Moyer, 1993 (76)	0M/11F	n.s.	19–25	Before and after lunch meal. Visual exposure and intake of chocolate chip cookies	Viewing and intake (1 cookie)	4 min visual, 8 min intake	Before lunch	n.s.	=	n.a.
							After lunch	n.s.	⇧⇧*	n.a.
Teff, 1993 (77)	15M/0F	24 ± 3	22.9 ± 0.9	Peanut butter sandwich	Fasting, MSF, intake	2 min	Fasting	=	=	n.a.
							MSF	=	⇧*	n.a.
							Intake	⇨	⇧⇧*	n.a.
Lam, 1993 (78)	7M/0F	18–25	n.s.	Mixed nutrient meal; hamburger, bread, margarine, tea	MSF	30 min	MSF mixed nutrient meal	=	n.a.	⇧⇧*
Teff, 1991 (18)	20M/0F	28 ± 5	n.s.	Aspartame-sweetened strawberry flavored gelatin with added dairy fat as a mousse	MSF	2 min	Day 1	=	⇧*	n.a.
							Day 2	=	⇧*	n.a.
							Day 3	=	⇧*	n.a.
Le Blanc, 1991 (79)	6M/0F	21–30	22.1 ± n.s.	Protein vs. carbohydrate; sugar pie vs. haddock fish	Intake	4 min	Sugar pie	⇨	⇧⇧*	n.a.
							Haddock fish	=	⇧⇧*	n.a.
Broberg, 1989 (39)	0M/4F	33 ± n.s.	n.s.	Seeing and description of a cinnamon roll	Thought and viewing	10 min	View and thought of cinnamon roll	n.a.	=	n.a.
Rini, 1987 (80)	5M/5F	33 ± 8	n.s.	2 saccharin tablets	Suck on tablet	5 min	Suck on 2 saccharin tablets	n.s.	⇨*	n.a.

(*Continued*)

TABLE 1 (*Continued*)

Study	N, male/female	Age, y, mean ± SD or range	BMI, kg/m^2, mean ± SD or range	Population and food cue specifics	Exposure to food cue	Exposure duration	Conditions	Effect on		
								Glu	Ins	PP
Lucas, 1987 (81)	3M/2F	21–27	n.s.	Onion tart or tuna tart or combination; repeated measures	Food intake	Freely	Day 1	⇨	⇧⇧	n.a.
							Day 2	⇨	⇧⇧	n.a.
Simon, 1986 (82)	2M/3F	26.7 ± 1.3	20.2 ± 0.5	Visual and smelling cue of a meal; raw carrots, fried chicken, spaghetti, and cookies	Visual and olfactory cue	15 min	Visual and smelling mixed meal	=	⇧*	n.a.
Osuna, 1986 (83)	0M/5F	22.5 ± 7	23.7 ± n.s.	Mixed meal breakfast; white coffee, butter toast, Danish roll	Visual and olfactory stimulation	5 min	Visual and olfactory exposure breakfast meal	=	⇧*	n.a.
Bellisle, 1983 (84)	3M/4F	20–25	n.s.	Mixed meal, low preferred item, high preferred food item; sandwich with crab, anchovies, liver paté, pork paté, and butter	Food intake (ad libitum)	Freely	Average of 42 meals	⇨	⇧⇧*	n.a.
Sjostrom, 1980 (42)	0M/22F	35 ± 6	21.23 ± n.s.	Tease meal (visual and smell cue) steak with fried onions, potatoes, vegetables, beer	Visual and olfactory stimulation	15 min	Visual and olfactory exposure mixed meal	n.s.	n.s.	n.a.
Overweight participants										
Eliasson, 2017 (85)	15M/0F	44.4 ± 8.4	26.2 ± 3.7	Vanilla caramel muffin	Intake	5 min max.	—	⇨	⇧⇧	n.a.
Buss, 2012 (4)	39M/0F	23.4 ± 0.5	23.2 ± 2.5	Sugar-free chewing gum	MSF	15 min	With or without visual + odor cue favorite breakfast	=	=	n.a.
Joosten, 2010 (86)	0M/22F	55.8 ± 2.7	26.3 ± 2.6	Sham feeding pound cake, white wine, or water	MSF	6 min	Cake	=	⇧	⇨
							Water	=	=	⇨
							White wine	=	=	⇨
Simon, 1986 (82)	7M/8F	33.3 ± 3.3	34.3 ± 1.4	Visual and smelling cue of a meal; raw carrots, fried chicken, spaghetti, and cookies	Visual and olfactory cue	15 min	Visual and smelling mixed meal	=	⇧*	n.a.
Obese participants										
Dhillon, 2017 (45)	23M/41F	27 ± n.s.	31.2 ± n.s.	Overweight and obese participants. MSF gelatin or drink with sucralose or sucrose	Rinse and MSF	15 sec every 2 min for 14 min	Nutritive solid-RS	=	⇧*	n.a.
							Nutritive solid-NR	=	=	n.a.
							Low cal. solid-RS	=	⇧*	n.a.
							Low cal. solid-NR	=	=	n.a.
							Nutritive liquid-RS	=	⇧*	n.a.
							Nutritive liquid-NR	=	=	n.a.
							Low cal. liquid-RS	=	⇧*	n.a.
							Low cal. liquid-NR	=	=	n.a.

(*Continued*)

TABLE 1 (*Continued*)

Study	N, male/female	Age, y, mean ± SD or range	BMI, kg/m^2, mean ± SD or range	Population and food cue specifics	Exposure to food cue	Exposure duration	Conditions	Effect on		
								Glu	Ins	PP
Morricone, 2000 (37) study 1	3M/9F	43.2 ± 4.2	39.1 ± 2.5	20 mg/10 mL saccharin/water solution and 5 mL lemon juice in 10 mL water. Control: water	Rinse	2 min	Saccharin, lemon, water	=	=	n.a.
Morricone, 2000 (37) study 2	1M/4F	40.3 ± 3.1	38.4 ± 4.3	Spaghetti, tomatoes, cheese, meat, salad, apple	Sight & smell, sight, smell alone	2 min	Only sight, only smell, sight & smell combined	=	=	⇧*
Karhunen, 1997 (87)	0M/10F	46.2 ± 11.3	33.1 ± 4.0	Nonbinge obese, mixed breakfast meal; ham, cheese, sausage, veggies, marmalade, artificially sweetened juice, coffee, tea	Anticipation and exposure, seeing breakfast & tasting juice	5 min anticipation, 17.5 min food exposure	Mixed breakfast meal	=	⇨	n.a.
Karhunen, 1996 (50)	8M/30F	44.2 ± 1.8	31–41	Breakfast meal; coffee/tea, orange juice, 4 sandwiches with ham cheese and veggies, and 2 chocolate cookies	Visual and olfactory cue	15 min	Pre WL RS	=	⇧	n.a.
							Pre WL INT	=	=	n.a.
							Pre WL NR	=	=	n.a.
							Post WL RS	=	⇧	n.a.
							Post WL INT	=	=	n.a.
							Post WL NR	=	=	n.a.
Lieverse, 1994 (49)	2M/12F	38 ± 2	42.4 ± 1.3	Mixed nutrient meal; hamburger, bread, mayonnaise	Intake	30 min	Mixed nutrient meal	⇨	n.a.	⇨
Osuna, 1986 (83)	0M/10F	31.6 ± 4.8	33 ± n.s.	Mixed meal breakfast; white coffee, butter toast, Danish roll	Visual and olfactory stimulation	5 min	Visual and olfactory exposure breakfast meal	=	=	n.a.
Sjostrom, 1980 (42)	0M/25F	45 ± 12	36.3 ± n.s.	Tease meal (visual and smell cue) steak with fried onions, potatoes, vegetables, beer	Visual and olfactory stimulation	15 min	Visual and olfactory exposure mixed meal	n.s.	n.s.	n.a.

(*Continued*)

TABLE 1 (*Continued*)

Study	N, male/female	Age, y, mean ± SD or range	BMI, kg/m^2, mean ± SD or range	Population and food cue specifics	Exposure to food cue	Exposure duration	Conditions	Effect on		
								Glu	Ins	PP
Parra-Covarrubias, 1971 (41)	4M/2F	13.1 ± n.s.	30–52	Obese to morbid obese children. Sight and smell of a breakfast meal of own choosing	Sight and smell	15 min	Sight and smell of preferred breakfast meal	=	⇧*	n.a.
Diabetic participants										
Eliasson, 2017 (85)	16M/0F	44.4 ± 8.4	26.2 ± 3.7	1st relative had diabetes, otherwise healthy participants. Food: muffin	Intake	5 min max.	Vanilla caramel muffin	⇨	⇧⇧	n.a.
LeBlanc, 1998 (70)	4M/3F	45 ± 4	29.3 ± 2.2	Noninsulin dependent diabetic participants, 250 g steak	Intake	Freely	Intake of steak	=	⇧⇧*	n.a.
Glasbrenner, 1995 (74)	14M/10F	43 ± n.s.	n.s.	DM with and without neuropathy. Preparation of a sandwich and MSF a sandwich with butter, bacon, and 2 scrambled eggs	Visual & smell, intake	10 min visual, 20 min MSF	Visual-DM	n.s.	n.a.	=
							Visual-NP	n.s.	n.a.	=
							MSF-DM	n.s.	n.a.	⇧
							MSF-NP	n.s.	n.a.	⇧
Participants with an eating disorder										
Bello, 2010 (48)	0M/22F	23.8 ± 4.6	21.9 ± 1.8	Bulimic participants, low-fat, half-fat, and full-fat yogurt with added fat-free cocoa	MSF	3 min	Nonfat placebo, fat placebo, fat naltrexone	=	=	*data not shown*
Karhunen, 1997 (87)	0M/11F	44.6 ± 9.7	32.8 ± 4.2	Binge eating obese, mixed breakfast meal ham, cheese, sausage, vegetables, marmalade, artificially sweetened juice, coffee, tea	Anticipation and exposure, seeing breakfast & tasting juice	5 min anticipation 17.5 min food exposure	Mixed breakfast meal	=	⇨	n.a.
Johnson, 1994 (38)	8F/0M	27.5 ± n.s.	20.4 ± n.s.	Bulimic participants. Mental imagery and viewing cookies and milk and induced purge	Thinking of and viewing	2/2 min	Cookies and milk	=	=	n.a.
Broberg, 1989 (39)	0M/4F	25.5 ± n.s.	n.s.	Anorexic participants. Seeing and description of a cinnamon roll	Thought and viewing	10 min	View and thought of cinnamon roll	n.a.	⇧*	n.a.
Moyer, 1993 (76)	0M/11F	n.s.	19–25	Bulimic participants. Before and after lunch meal. Visual exposure and intake of chocolate chip cookies	Viewing and intake (1 cookie)	4 min visual, 8 min intake	Before lunch	n.s.	=	n.a.
							After lunch	n.s.	⇧⇧*	n.a.

⇧ cephalic peak, ⇨ postabsorptive peak, ⇧⇧ preabsorptive peak (≤10 min) and postabsorptive peak, = no change from baseline, * significantly different from baseline ($P<0.05$). Conditions of the same study with the same outcome are summarized in 1 line. Cal, caloric; CHO, carbohydrate; DM, diabetes mellitus; Glu, glucose; Ins, insulin; INT, intermediate responder; MSF, modified sham feeding; MSG, monosodium glutamate; n.a., not assessed; NaCl, sodium chloride; NP, neuropathy; n.s., not specified; NR, nonresponder; PP, pancreatic polypeptide; QHCL, quinine-hydrochloride; RS, responder; WL, weight loss.

Overall quality of included studies.
See **Supplementary Figure 2** for the Cochrane risk of bias assessment graph. Out of the 53 included studies, 4 studies (8%) registered their trial and 4 (8%) performed a power calculation, 13 (25%) mentioned dropouts, and 17 (32%) performed compliance checks. From these 53 studies, 35 studies (66%) had a within-subject design, 7 (13%) had a within-subject between-groups design, and 11 (21%) had a between-subject design. Out of the 53 included studies, 43 studies (81%) had a proper control group or control condition.

To determine the quality of the studies, the Cochrane Collaboration's tool for assessing risk of bias was used. In total, 46 studies (87%) had a score below 5 and were considered at "low risk" of bias, 5 studies (9%) received a score between 4 and 5 and were considered at "medium risk" of bias, and 2 studies (4%) had scores above 5 and were considered to be at "high risk" of bias (Supplementary Figure 2).

Descriptive analysis.
Statistical analyses were performed using SPSS (BM Corp. released 2015; IBM SPSS Statistics for Windows, Version 23.0: IBM Corp.). Results are presented as the median ± IQR unless otherwise stated. P values <0.05 are considered statistically significant. To quantify an average response, time bins were created; time intervals were based on the average time intervals at which insulin and PP concentrations were measured in the original studies. **Figures 2** and **5** include only the study treatments that showed an increase in insulin ≥ 1 μIU/mL within the first 10 min and those that showed an increase in PP ≥ 10 pg/mL within the first 15 min after food cue onset.

The ≥ 1 μIU/mL cut-off for insulin is based on the smallest increase that we thought would suffice as a cephalic increase. This is also the smallest unit we could estimate using PDF ruler as the y-axes are usually expressed in units of 1 μIU/mL. Additionally, based on previous studies, we defined an insulin CPR to be an increase of ≥ 1 μIU/mL (16, 17, 19, 81). Similar to insulin, the cut-off for PP was based on the y-axes of most studies and as the PP cephalic response is described as a 100% increase from baseline (median baseline was 110 pg/mL) 10 pg/mL would also be the very minimum increase to be defined as a cephalic PP response.

Besides this, study treatments were included if they induced a significant increase from baseline according to the original study (even though the increase reported was <1 μIU/mL for insulin or <10 pg/mL for PP).

Results

CPIR

An increase in insulin ≥ 1 μIU/mL within 10 min after the food cue was observed in 41% ($n = 49$) of the treatments. The median (IQR) insulin increase based on the studies that showed ≥ 1 μIU/mL increase in insulin was 2.5 (1.6–4.5) μIU/mL at 5 ± 3 min after food cue onset. In 22% of all treatments (not using a 1 μIU/mL cut-off, $n = 119$) the rise was reported as statistically significant from baseline (Figure 2 and **Supplementary Table 1**).

A median insulin increase of 33% compared with baseline was observed within the first 10 min after the food cue (based on the studies that included a baseline concentration and treatments that induced ≥ 1 μIU/mL increase in insulin). A median increase of 60% was found when only including the treatments that induced a statistically significant increase from baseline. Excluding the treatments that involved actual food intake, baseline insulin increased 9% within the first 10 min after the food cue. The blood glucose concentration associated with these early insulin increases (≤ 10 min) did not change from baseline concentration with a median (IQR) concentration of 4.8 (4.5–5) mmol/L (**Figure 3** and **Supplementary Tables 2** and **3**).

Later than 10 min after the food cue, the median insulin concentration increased to 72% above baseline. Within this time frame glucose concentrations increased 15%. When the intake treatments were excluded there was no rise in insulin >10 min after food cue onset and glucose remained at baseline concentration (Figure 3 and Supplementary Tables 2 and 3).

Of the 49 treatments that increased insulin ≥ 1 μIU/mL, 18% were food anticipation treatments, 16% were induced by rinsing a solution, 31% by MSF, and 35% by actual food intake (Figure 2). The relative contribution of each type of treatment is shown in **Figure 4** and **Supplementary Table 4**.

The insulin response to food cues was measured in 57 subgroups (Supplementary Figure 1). In 61% of the 38 healthy normal-weight populations a CPIR was found, 37% of which were significantly different from baseline (according to the original study). Twelve studies measured insulin concentrations in overweight and obese participants; within this population, 5 studies found a CPIR of which 3 were significant. Three studies investigated CPIR in participants with (familial) diabetes; 2 found a CPIR of which 1 was significant. Five studies examined CPIR in participants with an eating disorder of which 2 found a significant response (Table 1).

CPPPR

In 48% ($n = 20$) of all treatments ($n = 42$), a PP increase >10 pg/mL within the first 15 min after the food cue was found. The median (IQR) PP increase was 99 (26–156) pg/mL from baseline, at 9± 4 min after food cue onset (based on the treatments that increased PP ≥ 10 pg/mL) (**Figure 5** and **Supplementary Table 5**). In 21% ($n = 9$) of all treatments (not using a 10 pg/mL cut-off, $n = 42$) a significant increase from baseline was found, according to the original study.

We found a median PP increase of 68% from baseline within the first 15 min after food cue onset (based on the treatments that increased PP ≥ 10 pg/mL). Excluding the treatments that involved actual food intake, the median PP increase was 17% from baseline within 15 min after food cue onset (**Figure 6** and **Supplementary Table 6**).

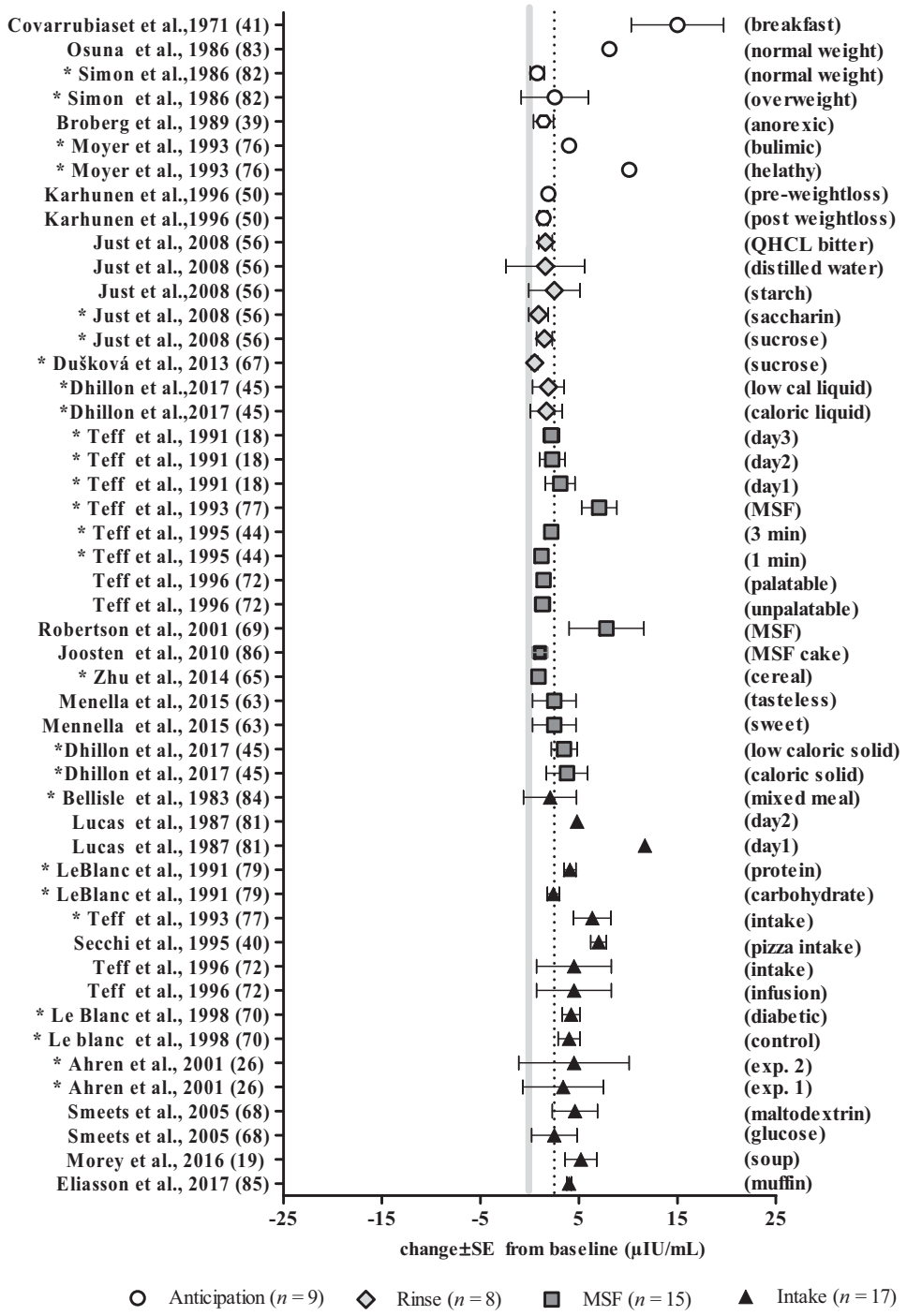

Figure 2 Overview of study treatment that found a cephalic insulin increase of ≥1 μIU/mL within 10 min (total $n = 49$, i.e., 41% of all included treatment conditions). Right column indicates treatment type, exposure duration, or subpopulation. ∗Indicates significance according to the original study ($n = 26$, 22%). The gray line indicates no change from baseline. The dotted line indicates the median change from baseline [median (IQR) = 2.5 (1.6–4.5) μIU/mL] over all studies. The different symbols indicate different treatment types. *N* indicates the number of study treatments. Cal, caloric; Exp., experiment; MSF, modified sham feeding; QHCL, quinine-hydrochloride. Values are means ± SEMs.

In the initial 15 min after the food cue we found a PP increase of 98% above baseline and this late increase in PP concentrations was not solely due to food intake treatments (Figure 6).

Of the 20 treatments that induced a PP response >10 pg/mL, 15% were food anticipation treatments, 60% were induced by MSF, and 24% by actual food intake (Figure 5). The relative contribution of each treatment type

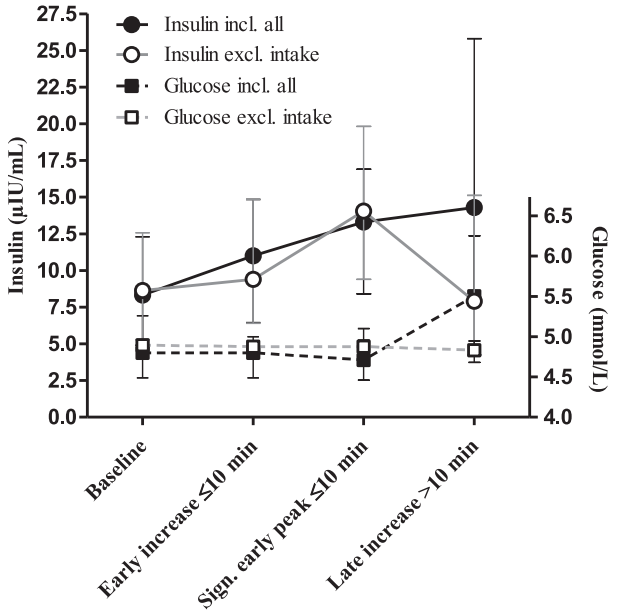

Figure 3 Insulin and glucose curves based on all included studies (including intake) and for studies not using food intake as treatment (excluding intake) showing baseline, early increase, significant early peak, and late increase (when increases were observed). Median ± IQR values can be obtained from Supplementary Table 2. The number of observations per graph point can be found in Supplementary Table 3. Values are medians ± IQR. excl., excluding; incl., including; Sign, Significant.

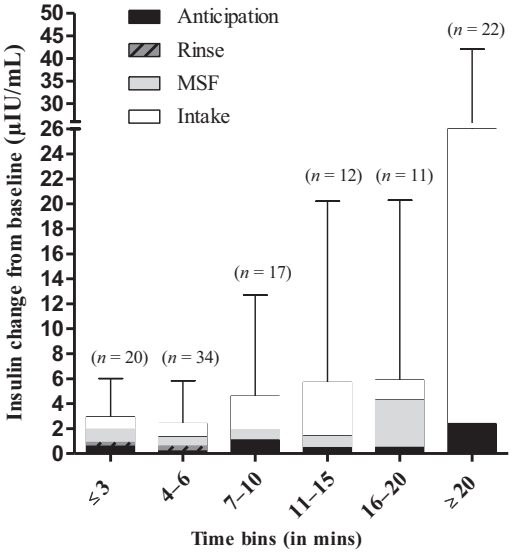

Figure 4 Insulin change from baseline per time bin. Differently colored bar segments indicate the percentage contribution of each treatment type. *N* indicates the number of study treatments included in that time bin. Values are the median ± 75th percentile. MSF, modified sham feeding.

per time bin is shown in **Figure 7** and **Supplementary Table 7**.

In 56% ($n = 7$) of the studies that included healthy participants with a normal BMI (18.5–25) a >10 pg/mL increase in PP was found; 19% were significant increases from baseline.

Three studies measured PP responses to a food cue in overweight and obese participants and 1 ($n = 5$) found a significant increase (200%) from baseline after exposure to the sight and smell of food (37). Only 1 study investigated cephalic PP responses in diabetic participants without autonomic neuropathy and found an increase similar to that observed in healthy controls (74). No such increase was observed in diabetic patients with autonomic neuropathy (74). We did not find studies examining cephalic PP responses in an eating disorder patient population (Table 1).

Relation between CPRs and food intake, and glucose homeostasis

Four studies investigated the relation between cephalic insulin responses and appetite or satiation (18, 19, 45,82). Teff et al. did not find any differences in ratings on hunger and motivation to eat, comparing hungry state with modified sham feeding. Furthermore, there was no correlation between appetite ratings and the magnitude of the CPIR (18). This is similar to the study of Simon et al., in which the significant CPIR after presentation of a meal did not correlate with hunger or habitual food intake (82). This is also in line with the finding of Morey et al. that satiety ratings do not differ between oral (with cephalic stimulation) and intubated feeding (no cephalic stimulation) (19). However, higher prospective consumption ratings for cephalic phase insulin responders compared with nonresponders were found, but these ratings did not correlate with the iAUC of insulin (45). Out of the 4 studies investigating the relation between cephalic insulin responses and appetite or satiation, only 1 study found indirect evidence (45).

To the best of our knowledge, only 1 study investigated the effect of a cephalic PP response on satiation. In this study, participants modified sham fed on a bitter (reduced CPPPR) or sweet pudding (greater CPPPR). PP responses after MSF on the sweet pudding were 23% greater compared with the bitter pudding, however, no differences in subsequent energy intake were observed (63).

Five studies investigated the relation between CPIR and postprandial glucose homeostasis (18, 69, 77, 82, 85). From these 5, 1 study found a CPIR along with a significant decrease in glucose (18), whereas 4 studies did not observe a concomitant decrease in glucose. These studies observed a CPIR after MSF on a peanut butter sandwich (77), after MSF on a fat meal (69), after presentation of a meal (82), and after eating a muffin (85).

Discussion

In this systematic review we found that 41% of the 199 included treatments triggered an insulin increase within 10 min after a food cue. In only 22% of all treatments was this rise reported as statistically significant by the original article. The median increase in insulin 5 min after the food cue was

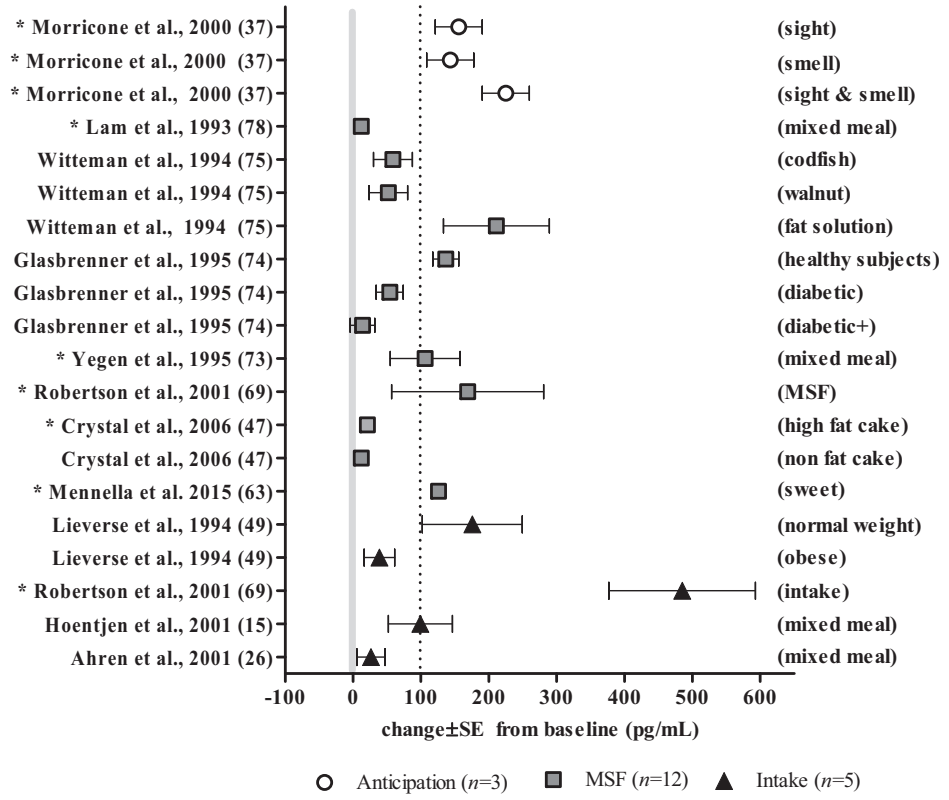

Figure 5 Overview of study treatments that found a cephalic pancreatic polypeptide increase of >10 pg/mL, within 15 min or when the increase was significant according to the original article ($n = 20$, 48%). Right column indicates treatment type, exposure duration or subpopulation. ∗Indicates significance according to the original study ($n = 9$, 21%). The gray line indicates no change from baseline. The dotted line indicates the median change from baseline [median (IQR) = 99 (26–156) pg/mL] over all studies. *N* indicates the number of study treatments. The different symbols indicate different treatment types. Values are means ± SEMs. MSF, modified sham feeding.

2.5 μIU/mL; this corresponded to a 30% increase compared with baseline, based on the median baseline concentration of 8.5 μIU/mL found in this review.

Whether this 30% increase at 5 min can be considered as a cephalic insulin response depends on the definition used. Three different definitions have been postulated. Teff et al. posited that a cephalic insulin increase 25% above baseline corresponded to a minimum increase of 2 μIU/mL insulin (16, 17). However, more than twice the magnitude of insulin increase (5 μIU/mL) from baseline is defined as a cephalic response by Morey et al. (19). Using their definition, the median increase of 2.5 μIU/mL would not be considered a cephalic response. Lucas et al. posited a definition that is not dependent on baseline concentrations (81). They defined a CPIR as a positive increase greater than twice the SD of spontaneous insulin fluctuations (81). Two types of nonfood-related insulin fluctuations have been described by previous studies: ultradian and pulsatile insulin fluctuations (88–94). Ultradian insulin fluctuations can easily be distinguished from cephalic increases as they occur within a relatively slow time interval of 48–96 min (95). However, pulsatile insulin fluctuations cannot be distinguished from a CPIR as these occur within a 5–17 min time interval, and thus overlap with the 10 min after a food cue during which cephalic responses are thought to occur (81). As CPIR cannot be distinguished from pulsatile insulin secretions based on time, the magnitude of the responses becomes most important to define a CPIR. The fluctuation amplitudes that have been reported range between 1.1 and 17 μIU/mL (56, 81). The median 2.5 μIU/mL increase we found falls well within this range and can therefore not be distinguished from naturally occurring fluctuations. According to these 3 definitions, which are all quite arbitrary, only the criterion of Teff et al. would define a median increase of 2.5 μIU/mL insulin from baseline as a CPIR (16, 17). A cephalic insulin response of this size would correspond to only 1% of the total postprandial insulin response (AUC) after a mixed nutrient meal (26). Besides this, less than half of the study treatments induced a rise in insulin to begin with, and in only a fifth was this increase significantly different from baseline, according to the original study. For these reasons, the evidence for the existence of a physiologically relevant CPIR seems minimal.

Fewer studies investigated the CPPPR; about half (48%) of the 42 included treatments induced a PP increase within the first 15 min after a food cue. In 21% of these, this increase was reported as being statistically significant from

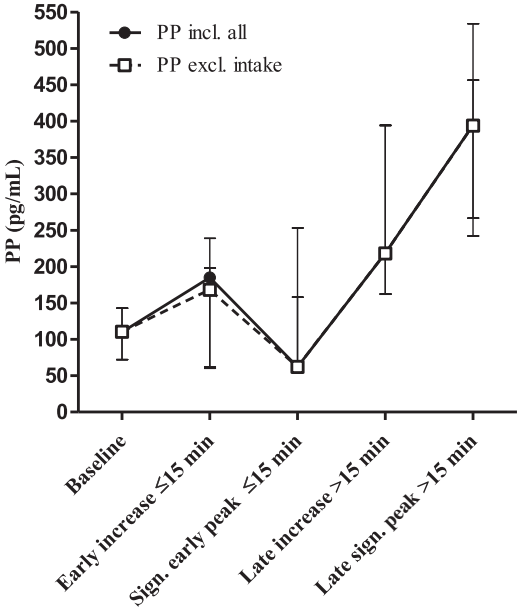

Figure 6 Change in pancreatic polypeptide per time bin based on all included studies (including intake) and for studies not using food intake as treatment (excluding intake). The number of observations per time point can be found in supplementary Table 6. Values are median ± IQR. excl., excluding; incl., including; PP, pancreatic polypeptide; sign., significant.

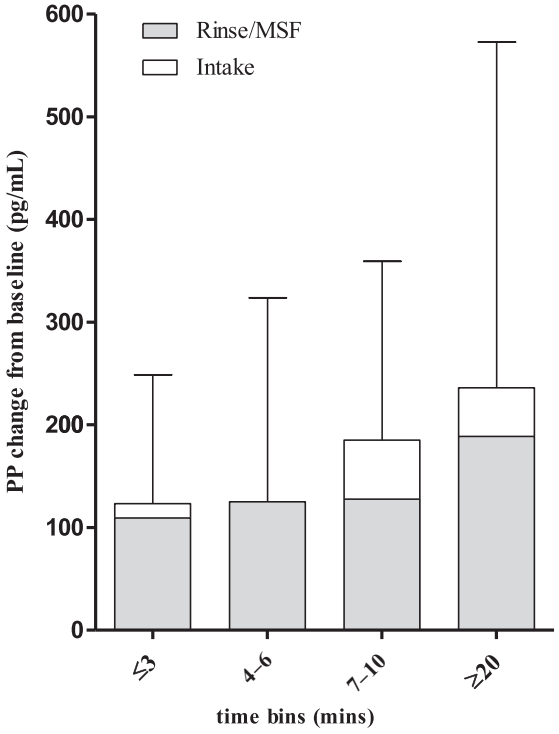

Figure 7 Pancreatic polypeptide change from baseline, per time bin. Differently colored bar segments indicate different treatment types. Modified sham feeding and rinse were combined due to the small number of studies. Values are median ± 75th percentile. MSF, modified sham feeding; PP, pancreatic polypeptide.

baseline. The median PP increase was 99 pg/mL (68%), 9 min after the food cue, meaning CPPPRs are much larger than CPIRs. Across studies, the median PP increase was 68% compared with baseline, which is substantially smaller than the 100% above baseline that is described as a cephalic PP response (96). However, it does correspond to 50% of the postnutrient uptake peak and can therefore be considered as a large response (15, 20). Although the magnitude of this median PP response can be considered as large, it exhibits high variability and it was only observed in half of the treatments included in this review, and only 23% of the increases significantly differed from baseline according to the original study. Therefore, CPPPR cannot be considered as a very robust phenomenon. This conclusion is supported by a study concluding that PP cannot be used as a marker of vagal stimulation to diagnose neuropathy in diabetic patients due to the high variability in PP responses (74).

The secondary aim of this review article was to determine whether responses occurred more frequently, or with a larger magnitude, for some types of food (cues) compared with others. Based on our classification of anticipation, rinsing, MSF, and intake treatments we found that the majority of the treatments that induced a CPIR and CPPPR were MSF and food intake treatments. This is in line with studies suggesting that multiple sensory modalities are needed to trigger a CPIR or CPPPR in humans (16, 45), but in contrast with observations from animal studies, where simple taste solutions consistently induce CPIR and CPPR. One of many explanations may be that humans have the cognitive ability to evaluate craving or wanting a food item. For other cephalic responses, such as salivation, it is known that they are most evident when a person is hungry and strongly craving the food item that they think of or is presented to them (97, 98). However, as yet, no research has been done on the direct relation between food craving and CPIR and CPPPR. Some studies have investigated the effect of craving indirectly and show that the magnitude of the CPIR and CPPPR is larger for palatable than nonpalatable food items (81, 79). That individuals have to like the food cue in order to elicit a CPIR or CPPPR explains why the response is not consistently found for the same food products in the same participants, as shown by Just et al. (56).

Taken together, the data show that CPIR and CPPPR can occur but not at all consistently. Therefore, if not due to nonfood-related fluctuations, they are highly specific and only occur in specific conditions in some individuals. One of our additional research questions was the occurrence of CPIR and CPPPR in specific subgroups. However, studies done in population groups such as overweight, obese, diabetic, or eating disorder groups are limited and therefore no answers could be given to this question.

Besides the weak evidence for human CPIRs and CPPRs we found no direct evidence for a relation between these responses and satiation or glucose homeostasis. Only 4 studies (18, 19, 45, 82) investigated the effect of a CPIR on

appetite or satiation, and only 1 of these found a relation between higher prospective consumption and a CPIR (45). One study investigated the effect of CPPPR on satiation (63). Tasting (without swallowing) a sweet pudding elicited a 23% greater CPPPR than tasting a bitter pudding, but no differences in energy intake were found in the subsequent meal (63).

The relation between cephalic responses and postprandial glucose homeostasis is especially of interest for people with diabetes. However, the hypothesized role of CPIR in glucose homeostasis is mostly derived from indirect evidence. For example, it has been suggested that oral sensory stimulation elicits a CPIR which influences glucose metabolism (25). By bypassing oral sensory stimulation, through nasogastric infusion of food, glucose and insulin concentrations increase more compared with food ingested normally (25, 62), suggesting a role of the CPIR in glucose homeostasis. Moreover, 2 studies, not included in this review as the CPIR was studied simultaneously with the infusion of dextrose (99) and trimethaphan (26), found direct evidence for a CPIR decrease in glucose. However, 5 studies (18, 82, 69, 77, 85) in our review investigated the direct relation between CPIR and glucose, and only 1 study found a CPIR 4 min after meal onset, along with a significant decrease in glucose (18). To summarize, there are only 3 studies that have shown a direct relation between a CPIR and glucose homeostasis, therefore evidence for an added value of CPIR in glucose homeostasis is limited. This may be due to compensatory behavior of glucagon or the gastric emptying rate to prevent nutrients from entering the bloodstream too fast (18, 62).

Besides the differences in food cue type and population studied, other methodological differences may explain the inconsistency between study findings. For example, the duration between placement of the catheter or cannula and blood sample collection. For instance, a study from Alvarez et al. showed that serum insulin concentrations increased 0.9 uIU/L $\leq$14 min after placement due to a stress response (100). Additionally, a wide range in the number of fasting hours before start of the intervention or food cue exposure was seen across the studies included; this may have caused differences in food craving and thus CPRs. Another methodological remark is that the measurements are highly dependent on the baseline fasting sample, therefore multiple baseline samples are needed to conclude whether the increase is due to the presented food cue or natural fluctuations (71). The vast majority of the studies only reported changes from baseline to correct for individual baseline differences. This is not in line with the advice of the Appetite Task Force of the International Life Sciences Institute to correct for baseline differences by means of ANCOVA rather than subtracting baseline (101, 102). Considering natural fluctuations over time in the baseline, variations in baseline are of interest and needed to draw conclusions. Especially in the case of repeated measures, the chances of a type I error increase and statistical significance is therefore not of primary interest. Instead, the size of the response relative to its (baseline) variation should be taken into consideration when drawing conclusions (103). The changes of a type I or II error depend on the sample size; only 8% of the studies did a power calculation prior to the study and the sample size in these studies ranged from 14 to 22 participants (4, 32, 66, 86). Future studies should take the above-mentioned methodological issues into account and focus on individual (phenotype) differences in food perception and appreciation in relation to cephalic insulin and PP responses.

Conclusions

About half of the treatments observed CPIRs and CPPPRs and of these, only a fifth found a statistically significant increase compared with baseline concentrations. The size of the CPIR increase (relative to spontaneous fluctuations) is small and there is substantial variation in magnitude and onset time of CPIRs and CPPPRs between food cues and individuals. Taking this into consideration, we conclude that there is little evidence for a physiologically relevant cephalic insulin or PP response. A large population-level study where insulin and PP concentrations can be measured continuously throughout everyday life is needed to confirm these conclusions. More importantly, the controlled laboratory setting in which CPRs have been studied to date make a translation to a natural and realistic food environment inherently difficult. We found little evidence that CPIRs or CPPPRs affect functional outcomes, that is, satiation and glucose homeostasis. Therefore, we conclude that cephalic insulin and PP responses do not seem to be biologically meaningful in daily life.

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