Food anticipatory hormonal responses

A systematic review of animal and human studies

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Food anticipatory hormonal responses: A systematic review of animal and human studies

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ABSTRACT

Food anticipatory hormonal responses (cephalic responses) are proactive physiological processes, that allow animals to prepare for food ingestion by modulating their hormonal levels in response to food cues. This process is important for digesting food, metabolizing nutrients and maintaining glucose levels within homeostasis. In this systematic review, we summarize the evidence from animal and human research on cephalic responses. Thirty-six animal and fifty-three human studies were included. The majority (88 %) of studies demonstrated that hormonal levels are changed in response to cues previously associated with food intake, such as feeding time, smell, and sight of food. Most evidence comes from studies on insulin, ghrelin, pancreatic polypeptide, glucagon, and c-peptide. Moreover, impaired cephalic responses were found in disorders related to metabolism and food intake such as diabetes, pancreatic insufficiency, obesity, and eating disorders, which opens discussions about the etiological mechanisms of these disorders as well as on potential therapeutic opportunities.

1. Introduction

Anticipatory physiological responses to food were first methodologically documented in the beginning of 20th century by the experiments of Ivan Pavlov. These experiments demonstrated that dogs react to stimuli associated with food with a release of saliva, gastric acid, and pancreatic enzymes (Pavlov, 1927). This phenomenon of learning an association between initially neutral stimuli and physiological responses, was called classical conditioning. At the same time, Pavlov introduced the term *cephalic response*, the classically conditioned metabolic responses aimed to prepare the organism for food ingestion (Pavlov, 1927, 1902). Cephalic response refers to the first stage of the food consumption, i.e., neural responses to the sensory cues related to food, such as the smell, taste, texture, and sight of food before the food gets ingested, or even to the context as time and location. Since then, the adaptive functions of the food anticipatory hormonal activity have been continuously studied.

Cephalic responses can be explained by the concept of allostasis: "a process by which an organism achieves internal viability through bodily changes" (Schulkin, 2003). Allostatic regulation, i.e. the ability of organisms to change their internal state in the anticipation of an event, is one of the important mechanisms of survival (Schulkin, 2011). To be successful in long-term survival, living organisms need not only to be able to react to the events that have already happened, but also to be able to predict and be prepare for the upcoming change. Cephalic responses are an example of such allostatic regulation (Power and Schulkin, 2008).

Several functions of the cephalic responses have been described in the literature. First, cephalic responses have been demonstrated to regulate feelings of hunger and satiety. Cues associated with the food, such as smell of food or the regular meals times and places, have been shown to increase appetite in humans and subsequently trigger

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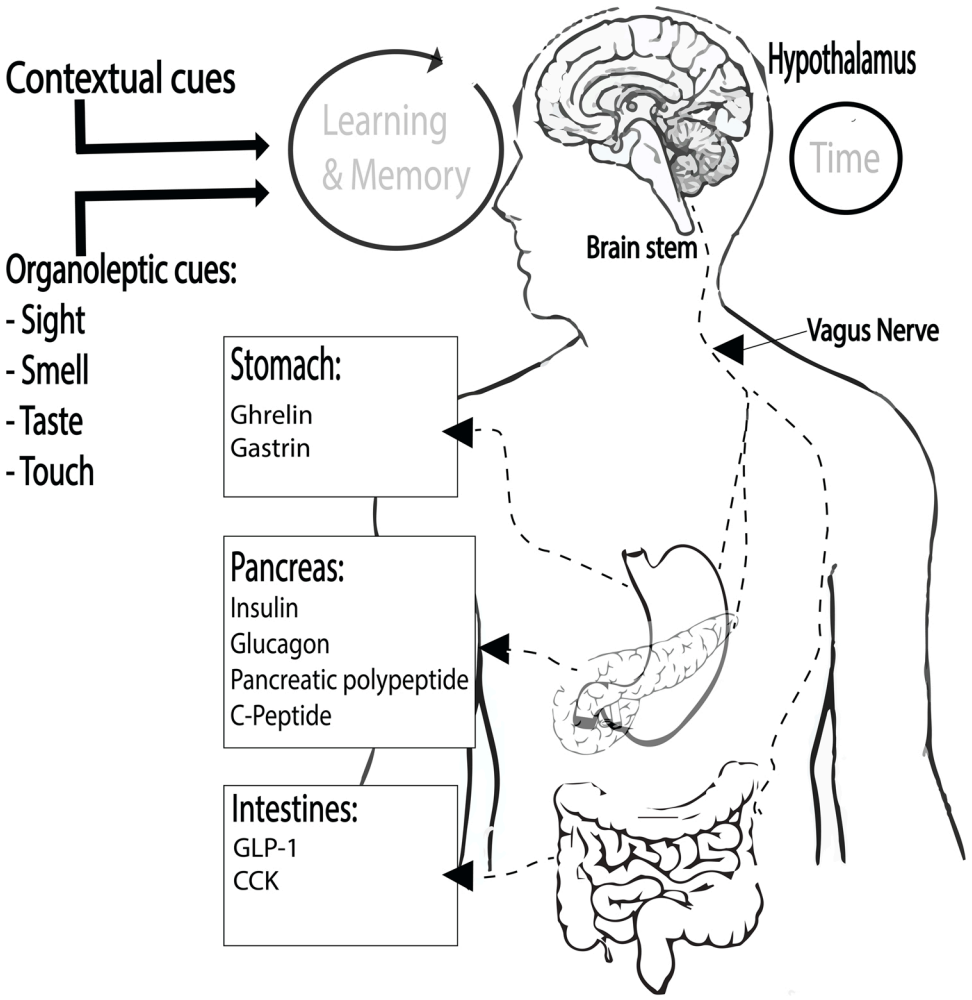

Fig. 1. Mechanisms of the food anticipatory hormone release.

salivation, ghrelin, gastric acid release and a cascade of hormonal changes (Johnson and Wildman, 1983; Yeomans, 2006). Animal research showed that in food deprived animals, cephalic responses to the smell of food trigger food search behavior (Lushchak et al., 2015). A review of Smeets and colleagues (Smeets et al., 2010) summarized evidence of the effects of the cephalic responses on hunger and satiety in humans. They concluded that cephalic release of insulin and ghrelin increase appetite, while cephalic release of cholecystokinin and leptin induce satiation.

By increasing appetite, cephalic insulin responses have been shown to allow organisms to consume larger meals (Woods, 1991); blocking cephalic insulin responses cause the decrease of the meal size eaten by animals and humans (Woods, 1991). Furthermore, cephalic responses prepare the digestive tract to process the nutrients in a more efficient way. They enable larger food intake, shorter time between food consumption, and, therefore, a greater rate of nutrients can be received from the environment (Giduck et al., 1987; Power and Schulkin, 2008). Food anticipatory hormonal responses play a crucial role in efficient digestion and absorption of nutrients while preventing potentially harmful changed in body due to the meal. Eating large amount of food has some hidden costs. After food consumption glucose levels rise rapidly and acute hyperglycemia might be a life-threatening state for an organism (Woods, 1991). Hyperglycemia has several adverse effects on the organism: chronic hyperglycemia and rapid glucose fluctuations are a major risk factor for diabetes, cardiovascular disorders (Colette and Monnier, 2007), and many types of cancer (Ryu et al., 2014). Food anticipatory hormonal effects help to prevent acute hyperglycemia by secreting glucose down-regulating hormones before the food digestion has started and therefore, maintaining glucose levels and the body homeostasis within the norms (Woods, 1991). Moreover, when food is delivered with an absence of cephalic responses, the digestion of food is prolonged (Pavlov, 1902), and the lipolysis is slowed down, which can lead to increased body weight (Yamashita et al., 1993).

Both top-down and bottom-up processes are involved in food anticipatory hormone releases which are produced by the central and peripheral nervous systems (see Fig. 1). It starts as a top-down process that is triggered by sensory cues related to food, such as smell, sight, taste of food, or by the time when the food is regularly delivered/accessible. Learning and memory mechanisms here play a central role as the association between these external stimuli and food has to be first learned. Upon recall, the central nervous system responds and modulates peripheral physiology via the vagus nerve mainly in two ways: 1) via the hypothalamus that controls the secretion of glucose counter-regulatory hormones, such as insulin, glucagon, c-peptide, and pancreatic polypeptide in the pancreas (Pozo and Claret, 2018), and 2) via the brainstem parasympathetic circuits that innervate the stomach and intestines which in turn secrete ghrelin, gastrin, glucagon-like peptide-1 and cholecystokinin (Herath et al., 1999; Storlien, 1985). In this way, the organism is prepared to down-regulate glucose levels right before the food starts being digested. Moreover, cephalic release of insulin and ghrelin triggers bottom-up signaling that induces hunger via the vagus nerve. These afferent and efferent signaling of the vagus nerve prepares the organism for the food intake and regulates the amount of food eaten. All these processes are additionally influenced by the circadian rythm:

Table 1
Overview of human studies.

	First author and year	Sample size (sex*)	Hormones (Conditioned Response)	Triggering stimulus (Conditioned Stimulus)	Experimental design	Results
1	Abdallah et al., 1997	12 (M)	Insulin, glucagon	Sweet taste	Cross-over; 3 conditions: sucking sucrose, aspartame-polydextrose, unsweetened polydextrose	Insulin: n.s. in all conditions Glucagon: n.s. in all conditions
2	Ahrén and Holst, 2001	12 (F)	Insulin, gastric inhibitory polypeptide, glucagon-like peptide-1	Food consumption	Cross-over; 3 conditions: trimethaphan, atropine, saline injection	Insulin: preprandial increase in saline group. Gastric inhibitory polypeptide: n.s. Glucagon-like peptide 1: n.s.
3	Arosio et al., 2004	16 (7 M, 9 F)	Ghrelin, insulin, pancreatic polypeptide	Sham feeding	Between-subjects; 2 conditions: full meal, modified sham feeding	Ghrelin: preprandial decrease in both groups from baseline Insulin: n.s. Pancreatic polypeptide: preprandial increase in both groups from baseline
4	Bellisle et al., 1983	7 (4 F, 3 M)	Insulin	Food consumption	Within-subjects	Insulin: preprandial increase from baseline
5	Bellisle et al., 1985	10 (4 M, 6 F)	Insulin	Expectation of food	Cross-over; 3 conditions: food condition, expectation of food, no expectation of food	Insulin: preprandial increase in food expectation and food conditions (only for high-palatable food) in comparison to the no expectation condition
6	Brede et al., 2017	40 (M)	Glucagon, insulin, c-peptide	Food pictures	Between-within 2 × 2: normal weight vs obese; food pictures vs non-food pictures	Glucagon, insulin, c-peptide: n.s.
7	Broberg and Bernstein, 1989	8 (F)	Insulin	Food consumption	Between-subjects; 2 conditions: patients with anorexia, healthy controls	Insulin: preprandial increase in anorexia condition from baseline. N.s. in the healthy control condition
8	Bruce et al., 1987	18 (14 M, 4 F)	Insulin	Expectation of food, sweet taste	Between-subjects; 3 conditions: tease feeding (expecting food), sweet taste, combined	Insulin: increase in the combined condition compared to other conditions
9	Buss et al., 2012	39 (M)	Insulin, pancreatic polypeptide	Presentation of favorite food	Between-subjects; 2 conditions: food presentation, control	Insulin: n.s. Pancreatic polypeptide: increase in food presentation condition compared to the control condition
10	Buysschaert et al., 1985	16 (8 M, 8 F) patients with type-1 and type-2 diabetes, 8 (4 M, 4 F) healthy controls	Pancreatic polypeptide	Sham feeding	Between-subjects, 3 groups: healthy controls, diabetes patients with cardiac autonomic neuropathy, diabetes patients without cardiac autonomic neuropathy	Pancreatic polypeptide: increase in healthy controls and patients without cardiac autonomic neuropathy compared to diabetes patients with cardiac autonomic neuropathy
11	Cedernaes et al., 2016	16 (M)	Insulin	Oral rinsing with glucose solution	Cross-over; 2 conditions: sleep deprivation, full sleep	Insulin: n.s. in both groups
12	Crum et al., 2011	46 (16 M, 30 F)	Ghrelin	Food expectation	Cross-over; 2 conditions for all participants: "indulgent" shake label, "sensible" shake label	Ghrelin: decrease in "indulgent" shake label condition compared to "sensible" shake condition
13	Crystal and Teff, 2006	22 (F)	Insulin, glucagon, pancreatic polypeptide	Sham feeding	Between-subjects, 2 × 3: restrained vs non-restrained eaters in 3 conditions: fasting, sham feeding a low-fat cake, sham feeding a high-fat cake	Pancreatic polypeptide: increase in a high-fat condition compared to fasting control in both restrained and unrestrained eaters Insulin: n.s. Glucagon: n.s.
14	Cummings et al., 2001	10 (1 M, 9 F)	Ghrelin, insulin, leptin	Standard eating time	Within-subjects	Ghrelin: increase before food time, decrease after food consumption Insulin: increase before food time and after food consumption Leptin: n.s.
15	Dhillon et al., 2017	64	Insulin	Sweet taste	Between-subjects; 2 × 2: nutritive sweetener (sucrose) vs low calorie sweetener (sucralose); liquid vs solid form.	Insulin: increase in sucrose and sucralose conditions from baseline. Solid form higher than liquid form.
16	Eliasson et al., 2017	31 (M)	Insulin and c-peptide	Food consumption	Between-subjects; 2 conditions: family history with diabetes type-2, without	Insulin: increase in both groups from baseline C-peptide: increase in both groups from baseline
17	Feldman and Richardson, 1986	13 (10 M, 3 F)	Gastrin	Discussion about food	Cross-over; 6 conditions: discussion of food, discussion	Gastrin: Increase in all conditions from baseline. Modified sham

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Table 1 (*continued*)

	First author and year	Sample size (sex*)	Hormones (Conditioned Response)	Triggering stimulus (Conditioned Stimulus)	Experimental design	Results
					of other topic, sight of food, smell of food, sight and smell combined, modified sham feeding	feeding condition- the highest increase compared to other conditions
18	Frecka and Mattes, 2008	21 (13 M, 8 F)	Ghrelin, insulin	Standard eating time	Between-subjects; 2 conditions: short intermeal interval feeding pattern, long intermeal interval feeding pattern	Ghrelin: increase prior expected lunch in both groups from baseline
19	Glasbrenner et al., 1995	57 (32 M, 25 F)	Pancreatic polypeptide	Sham feeding	Between-subjects; 3 conditions: healthy controls, diabetes patients with cardiac autonomic neuropathy, diabetes patients without cardiac autonomic neuropathy	Pancreatic polypeptide: increase in all groups from baseline. Increase in healthy controls significantly larger than in diabetes patients. Increase in patients without autonomic neuropathy is higher than in patients with autonomic neuropathy
20	Goldschmiedt et al., 1990	12 (7 M, 5 F)	Gastrin	Sham feeding	Cross-over, 3 conditions: unusual food coloring, ordinary food coloring, no food coloring.	Gastrin: increase in all conditions from baseline
21	Härtel et al., 1993	14 (6 M, 8 F)	Insulin	Sweet taste	Cross-over; 6 conditions: aspartame, acesulfame-k, cyclamate, saccharin, a sucrose solution, water	Insulin: n.s.
22	Johnson and Wildman, 1983	6 normal weight (5 M, 1 F), 4 obese (3 M, 1 F)		Presentation of food and imagining eating	Cross-over; 2 conditions: presentation of food, imagining eating favorite food	Insulin: increase in both conditions compared to baseline. Greater response in obese participants compared to normal weight participants.
23	Just et al., 2008	5 (2 M, 3 F)	Insulin	Sweet taste	Cross-over; 8 conditions: rinsing mouth with: sucrose, saccharin, acetic acid, sodium chloride, quinine hydrochloride, distilled water, starch, and sodium glutamate	Insulin: increase in sucrose and saccharine conditions compared to other conditions
24	Lasschuijt 2018	18 (M)	Insulin, pancreatic polypeptide, ghrelin	Sham feeding	Cross-over 2 × 2 plus a control: sham feeding two levels of processing time (soft vs hard texture), and two concentrations of sweetness (low vs high) plus control without feeding	Insulin, pancreatic polypeptide, ghrelin: n.s.
25	Mennella et al., 2015	20 (9 M, 11 F)	Pancreatic polypeptide, ghrelin	Sham feeding	Cross-over, 3 conditions: sweet, control, bitter pudding	Ghrelin: increase in the control pudding condition compared to sweet and bitter conditions Pancreatic polypeptide: higher in sweet than in bitter condition
26	Monteleone et al., 2008	16 (F)	Ghrelin, obestatin	Sham feeding	Between-subjects; 2 conditions: anorexia patients, healthy controls	Ghrelin: increase in both conditions from baseline; increase in anorexia patients compared to healthy controls. Obestatin: decrease in both conditions from baseline; decrease in anorexia patients compared to healthy controls
27	Monteleone et al., 2010	13 (F)	Ghrelin	Sham feeding	Between-subjects; 2 conditions: bulimia patients, healthy controls	Ghrelin: increase in both conditions from baseline; increase in bulimia patients compared to health controls
28	Morricone et al., 2000 Experiment 1	12 (3 M, 9 F)	Pancreatic polypeptide, insulin	Sweet taste	Cross-over; 3 conditions: oral rinse with saccharine, lemon juice, water	Pancreatic polypeptide: n.s. Insulin: n.s.
	Morricone et al., 2000 Experiment 2	5 (1 M, 4 F)	Pancreatic polypeptide, insulin	Food cues	Cross-over; 3 conditions: sight and smell, sight only, smell only	Pancreatic polypeptide: increase in all conditions from baseline Insulin: n.s.
29	Moyer et al., 1993	22 (F)	Insulin, epinephrine, norepinephrine	Presentation of food	Between-within subjects, 2 × 2: patients with bulimia, healthy controls; 2 presentations of food	Insulin: increase during 2nd presentation in both groups compared to the first presentation Epinephrine,: n.s. Norepinephrine: n.s.
30	Osuna et al., 1986	15 (F)	Insulin	Presentation of food		Insulin: increase in healthy controls compared to obese patients

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Table 1 (*continued*)

	First author and year	Sample size (sex*)	Hormones (Conditioned Response)	Triggering stimulus (Conditioned Stimulus)	Experimental design	Results
					Between-subjects; 2 conditions: obese and healthy controls	
31	Ott et al., 2011	29 (M)	Insulin, cortisol, adrenocorticotropin (ACTH), leptin and ghrelin	Expectation of food	Between-subjects; 2 conditions: food anticipation, no anticipation	Cortisol: increase in anticipation condition compared to no anticipation condition Insulin, leptin, ghrelin, ACTH: n.s.
32	Ott et al., 2012	29 (M)	Ghrelin, pancreatic polypeptide, leptin	Presentation of food	Between-subjects; 2 conditions: announcement and presentation of meal, control (remained fasting)	Ghrelin,: n.s. Pancreatic polypeptide: n.s. Leptin: n.s.
33	Parra-Covarrubias et al., 1971	6 (4 M, 2 F) obese adolescents	Insulin	Presentation of food	Within-subjects	Insulin: increase from baseline
34	Rigamonti et al., 2015	10 (M) obese	Ghrelin, glucagon-like peptide-1, peptide YY, anandamide, 2-arachidonoyl-glycerol, palmitoylethanolamide, oleoylethanolamide	Expectation of food	Cross-over; 2 conditions: palatable food, non-palatable food	Ghrelin: increase in both conditions from baseline Anandamide: increase in both conditions from baseline 2-AG: increase in both conditions from baseline Oleoylethanolamide: increase in palatable food condition compared to non-palatable condition Other: n.s.
35	Sahakian et al., 1981	14 (10 M, 4 F)	Insulin, glucagon	Presentation of palatable food	Within-subjects	Insulin: preprandial increase from baseline Glucagon: n.s.
36	Schwartz et al., 1979	34	Pancreatic polypeptide	Sham feeding	Between-subjects; 2 conditions: duodenal ulcer patients and healthy controls	Pancreatic polypeptide: increase in both conditions from baseline
37	Schüssler et al., 2012	8 (M)	Ghrelin	Consumption of food	Cross-over: 2 conditions: neutral pictures, food pictures presentation	Ghrelin: increase 30 min following presentation of food pictures compared to control pictures
38	Secchi et al., 1995	10	Insulin, glucagon	Consumption of food	Between-subjects; 2 conditions: kidney and pancreas transplanted patients, healthy controls	Insulin: increase in healthy controls compared to patients Glucagon: increase in healthy controls compared to patients
39	Smeets et al., 2005	5 (M)	Insulin	Sweet taste	Cross-over: water, glucose, aspartame, maltodextrin (nonsweet carbohydrate)	Insulin: increase in glucose and maltodextrin groups conditions to water and aspartame conditions
40	Simon et al., 1986	25 (12 M, 13 F)	Insulin	Presentation of food	Between-subjects; 2 conditions: obese and normal weight	Insulin: increase in both groups from baseline
41	Simonian et al., 2005	15 (6 M, 9 F)	Pancreatic polypeptide, ghrelin, insulin	Sham feeding followed by food consumption	Within-subjects	Ghrelin: increase from baseline Pancreatic polypeptide: increase from baseline Insulin: n.s.
42	Sjöström et al., 1980	25 obese (F), 23 normal weight (F)	Insulin, cortisol, glucagon	Presentation of food	Between-subjects; 3 conditions: obese, normal weight, atropine obese	Insulin: increase in the obese group in comparison to the normal weight group and atropine obese group Cortisol: n.s. Glucagon: n.s.
43	Teff et al., 1991	20 (M)	Insulin	Sham feeding	Within-subjects; 3 trials	Insulin increase from baseline
44	Teff 1993a	15 (M)	Insulin, c-peptide, norepinephrine, epinephrine	Sham feeding	Cross-over; 3 conditions: modified sham feeding, food consumption, fasting	Insulin, c-peptide increase in modified sham feeding and food consumption conditions compared to fasting Norepinephrine, epinephrine : n.s.
45	Teff 1993b	33 (M)	Insulin	Sham feeding	Between-subjects; 2 groups: heathy weight and obese men	Insulin increase in both groups from baseline
46	Teff et al., 1995 Experiment 1	15 (M)	Insulin	Sham feeding	Cross-over; 5 conditions: water, aspartame solution, saccharine solution, sucrose solution, apple pie	Insulin: increase in apple pie condition compared to other conditions
	Experiment 2	16 (M)	Insulin	Sham feeding	Cross-over; 5 conditions: water, aspartame solution, saccharine solution, sucrose solution, apple pie. Tasting for 3 minutes	Insulin: increase in apple pie condition compared to other conditions
47	Teff and Engelman, 1996a	13 (F)	Insulin	Sham feeding	Cross-over; 2 conditions: palatable, non-palatable food	Insulin: increase in both conditions from baseline
48	Teff and Engelman, 1996b	8 (M)	Insulin, c-peptide, glucagon	Sham feeding		Insulin: increase in the modified sham feeding condition compared

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Table 1 (*continued*)

	First author and year	Sample size (sex*)	Hormones (Conditioned Response)	Triggering stimulus (Conditioned Stimulus)	Experimental design	Results
					Cross-over; 2 conditions: modified sham training, fasting	to fasting C-peptide: increase in the modified sham feeding condition compared to fasting Glucagon: increase in the modified sham feeding condition compared to fasting
49	Teff, 2010 Experiment 1	10 (5 M, 5 F)	Pancreatic polypeptide	Sweet taste	Cross-over; 3 conditions: fasting, tasting a sweet glucose solution, tasting a salty solution	Pancreatic polypeptide: n.s.
	Teff, 2010 Experiment 2	15 (11 M, 4 F)	Pancreatic polypeptide	Chewing gum	Cross-over; 4 conditions: fasting, chewing an unflavored, unsweetened gum base, chewing a gum base sweetened with a non-nutritive sweetener, chewing a gum base flavored with mint and sweetened with a non-nutritive sweetener	Pancreatic polypeptide: n.s.
	Teff, 2010 Experiment 3	12 (6 M, 6 F)	Pancreatic polypeptide	Sham feeding	Cross-over; 5 conditions: fasted, sham- feed palatable sweet food, sham-feed unpalatable sweet food, sham-feed salty palatable food, sham-feed salty unpalatable foods	Pancreatic polypeptide: increase in all sham-feeding conditions compared to fasting
50	Veedfald et al., 2016	10 (M)	Insulin, c-peptide, glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1	Sham feeding	Cross-over; 2 conditions: modified sham feeding, control	Insulin, c-peptide, glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1: n.s.
51	Wøjdemann et al., 2000	16 (11 M, 5 F)	Gastrin, secretin, cholecystokinin, pancreatic polypeptide	Sham feeding	Between-subjects; 2 conditions: patients with pancreatic insufficiency, healthy controls	Secretin: increase in healthy controls compared to patients Gastrin, cholecystokinin, pancreatic polypeptide: n.s.
52	Yamazaki and Sakaguchi, 1986	57 (M)	Insulin	Sweet taste of glucose on the tongue	Cross-over; 3 conditions: solution of d-glucose, sham, d-glucose with atropine	Insulin: increase in d-glucose condition compared to other conditions
53	Zhu et al., 2014	10 (M)	Insulin, ghrelin	Sham feeding	Cross-over; 4 conditions: water, high-fat, high-carbohydrate, high-protein food	Insulin: increase in high-carbohydrate compared to other conditions Ghrelin: increase in the high-protein food condition compared to other conditions

Note. M- male, F- female, * In case no sex is given in the table, it was not available in the original article; n.s.- not significant.

the food anticipatory responses do not emerge when the feeding intervals are outside of circadian range of 22−31 hours (Aschoff, 1991; Mistlberger, 1994).

To test the working mechanisms of food anticipatory activity, anticipatory hormonal responses have been studied with respect to various feeding and eating patterns, cues, and foods in both animals and humans. Despite the large number of studies done in this field, particularly between the middle to end of the 20th century, surprisingly, to our knowledge, no study summarized results of both animal and human studies while additionally including evidence on various hormonal outcomes. Although, several papers described the literature in a non-systematic manner (Hadamitzky et al., 2019; Power and Schulkin, 2008; Teff, 2011; Woods, 2002; Zafra et al., 2006). Also, a recent systematic review presented human studies on the anticipatory insulin and pancreatic polypeptide responses (Lasschuijt et al., 2020), and another recent meta-analysis focused on anticipatory insulin responses in humans (Wiedemann et al., 2020). Interestingly, these two recent papers present contradictory conclusions with Lasschuijt (Lasschuijt et al., 2020) stating that cephalic responses have no meaningful biological effects in humans, while Wiedemann et al. (2020) concluding that there is convincing evidence for the presence of cephalic insulin responses in humans.

The main goal of this review is to give for the first time a systematic overview of experimental studies on food anticipatory hormone release in animals and humans (both healthy and clinical populations). We summarize the findings in the field, describe what hormonal responses were investigated in the context of anticipatory release, and what is known about cephalic responses in clinical samples. Additionally, we describe experimental designs used in this field of research, stimuli that trigger anticipatory hormone release, and the underlying mechanisms of this phenomenon. As food anticipatory hormone responses play a crucial role in metabolism, understanding this phenomenon might shed more light to both healthy functioning of an organism and processes involved in various metabolic disorders.

2. Methods

2.1. Protocol

The data for this review were collected as part of a larger systematic search of literature on classical conditioning of endocrine responses. The review protocol was registered on PROSPERO (registration number CRD42017058783). From the total number of studies found in this literature search, experimental studies on classical conditioning of

Table 2
Overview of animal studies.

	Authors and year of the paper	N of subjects, specie, sex*	Hormone	Triggering stimulus	Design	Results
1	Bernstein and Woods, 1980 Experiment 1	43 rats	Insulin	Taste of saccharine	Between-within subjects 4 × 2; 4 age conditions: 21−22 day old, 34 day old, 45 day old, adults; 2 foods: saccharine and control	Insulin: increase in all age conditions compared to baseline
	Experiment 2	22 newborn rats	Insulin	Taste of saccharine	Between-subjects; 2 conditions: saccharine and control	Insulin: n.s.
2	Berthoud et al., 1980a	Rats (M)	Insulin	Taste of saccharine	Cross-over; 6 conditions with prior ventromedial hypothalamus injection of either: 2 × 1 ~1 saline, 2 × 15 pg neutralized procaine HCl, 2 × 50 pg neutralized procaine HCl	Insulin: increase in saline condition compared to other conditions; decrease in 2 × 15 pg neutralized procaine HCl condition and 2 × 50 pg neutralized procaine HCl condition compared to other conditions
3	Berthoud et al., 1980b	Rats (M)	Insulin	Taste of saccharine	Between-subjects; 4 conditions: saccharine, glucose, tap water, no stimulus	Insulin: increase in saccharine and glucose conditions compared to tap water and no stimulus conditions
4	Berthoud et al., 1981	Rats (M)	Insulin	Taste of saccharine	Between-subjects; 3 conditions: saccharine, tap water, quinine	Insulin: increase in saccharine group compared to other conditions
5	Berthoud and Jeanrenaud, 1982 Experiment 1	7 rats	Insulin	Taste of saccharine	Cross-over; 5 conditions: sham feeding + saline injection, sham feeding + atropine; feeding + saline, feeding + atropine; no feeding	Insulin: increase in saline conditions compared to atropine and no feeding conditions.
	Experiment 2	5 rats	Insulin, glucagon	Taste of saccharine	Cross-over; 3 conditions: sham feeding; feeding; fasting	Insulin: increase in sham feeding and feeding conditions compared to fasting Glucagon: increase in sham feeding and feeding conditions compared to fasting
	Experiment 3	7 rats	Insulin	Taste of saccharine	Cross-over; 5 conditions: sham feeding + saline injection, sham feeding + phentolamine; feeding + saline, feeding + phentolamine; no feeding	Insulin: increase in sham feeding. Phentolamine enhanced this response
6	Berthoud and Powley, 1990	Rats (M)	Insulin	Food consumption	Cross-over; 4 conditions: milk, lab chow, glucose, sodium saccharine	Insulin: increase from baseline 2 min after the start in all conditions
7	Coover et al., 1984	70 rats (M)	Corticosterone	Sound of room entry and time of feeding	Between-within subjects 2 × 2: immediately fed, fed after delay; day 17, day 20	Corticosterone: day 7- increase in delayed fed group from baseline; day 20- decrease in immediately fed from baseline
8	Dailey et al., 2012	42 rats	Insulin, ghrelin, glucagon-like peptide-1	Time of feeding	Between-within subjects 3 × 2; 3 meal conditions: chow, high-fat, chocolate; 2 feeding conditions: meal fed, ad libitum	Insulin: increase in chow meal fed and high-fat meal fed conditions compared to other conditions Ghrelin: increase in chow meal fed and high-fat meal fed groups compared to other conditions Glucagon-like peptide-1: increase in in chow meal fed and high-fat meal fed groups compared to other conditions
9	Davidson and Stephan, 1999	Rats (M)	Insulin, glucagon, and motilin	Time of feeding	Between-subjects; 3 conditions: intact rats, rats with suprachiasmatic nucleus lesion, controls	Insulin: n.s. Glucagon: decrease in lesion and controls groups compared to intact Motilin: n.s.
10	De Souza et al., 2001	Rats (M)	Insulin	Food consumption	Between-subjects; 3 conditions: nateglinide, glipizide, repaglinide	Insulin: increase in all conditions compared to baseline
11	Diamond and LeBlanc, 1988	5 dogs	Insulin	Food consumption	Cross-over; 3 conditions: saline injection, atropine sulfate injection, denervation of pancreas	Insulin: Increase in saline group compared to other groups
12	Drazen et al., 2006	Rats (M)	Ghrelin	Time of feeding	Between-subjects; 2 conditions: freely fed rats and meal fed at certain times	Ghrelin: increase in meal-fed before the time of feeding compared to freely fed
13	Flatt and Bailey, 1983	Rats (M)	Insulin	Time of feeding	Between-subjects; 4 conditions: conditioned obese, control obese, conditioned lean, control lean	Insulin: n.s.
14	Fischer et al., 1972	22 (9 M, 13 F) dogs	Insulin	Food consumption	Cross-over; 4 conditions: injection of glucose, injection of NaCl, oral glucose, oral water	Insulin: increase in the oral glucose condition compared to other conditions
15	Glendinning et al., 2017	Mice	Insulin	Sweet taste	Between-subjects; 10 conditions: glucose, sucrose, maltose, fructose, polycose, saccharin, sucralose, AceK, SC45647, a nonmetabolizable sugar analog	Insulin: increase in glucose, sucrose, maltose, and polycose conditions compared to other conditions
16	Glendinning et al., 2018 Experiment 1	Mice	Insulin	Intragastric glucose administration	Within-subjects	Insulin: n.s.
	Experiment 2	Mice	Insulin	Sweet taste	Between-subjects, 2 conditions: 1 M glucose, 1 M glucose+5 mM acarbose	Insulin: increase in both conditions from baseline
17	Herath et al., 1999 Experiment 1	26 wethers (F)	Insulin	Food presentation	Between-subjects; 3 conditions: abomasal, pyloric and duodenal	Insulin: increase in sham operation condition compared to other conditions

(*continued on next page*)

Table 2 (*continued*)

	Authors and year of the paper	N of subjects, specie, sex*	Hormone	Triggering stimulus	Design	Results
					vagotomy; hepatic, abomasal, pyloric and duodenal vagotomy; sham-operation	
	Experiment 2	10 lactating ewes (F)	Insulin	Lactation cues	Between-subjects; 2 conditions: abomasal, pyloric and duodenal vagotomy; sham-operation	Insulin: increase in sham operation condition compared to other conditions
18	Holmes et al., 1989	Rats (M)	Insulin	Glucose consumption	Between-subjects; 2 conditions: scheduled feeding and control	Insulin: increase in the scheduled feeding group compared to control
19	Karmann et al., 1992	7 geese	Insulin	Food consumption	Within-subjects	Increase in insulin at the start of feeding
20	Konturek et al., 1990	20 dogs	Gastrin, pancreatic polypeptide, cholecystokinin	Sham feeding	Between-subjects; 3 conditions: teasing, sham feeding, control	Gastrin: increase in teasing and sham feeding compared to control Pancreatic polypeptide: increase in teasing and sham feeding compared to control Cholecystokinin- n.s.
21	Kovacs et al., 1997	4 dogs	Gastrin	Sham feeding	Between-subjects; 3 conditions: gastrin monoclonal antibody, keyhole limpet hemocyanin monoclonal antibody (control), atropine	Gastrin increased in all conditions compared to baseline
22	Li et al., 2015	Wild-type mice (M, F)	Ghrelin	Time of feeding	Between-subjects 4 × 2; 4 sex hormones conditions: male gonadectomized, female gonadectomized, male controls, female controls; 2 feeding conditions: ad libitum, restricted feeding	Ghrelin increased in restricted feeding. Ghrelin increased in ad libitum fed female controls compared to ad libitum fed male controls.
23	Louis-Sylvestre, 1976	22 rats	Insulin	Glucose consumption	Between-subjects; 2 groups: drinking glucose solution, intragastric administration of glucose solution	Insulin: earlier increase in the drinking group than in the intragastric administration group
24	Lushchak et al., 2015	Drosophila flies (F)	Insulin like peptides	Smell of cider vinegar	Between-subjects; 2 conditions: cider vinegar smell, distilled water	Upregulation of genes encoding the glucagon-like hormone adipokinetic hormone, and insulin-like peptides in cider vinegar condition compared to water condition
25	Moberg et al., 1975 Experiment 1	Rats (M)	Corticosterone, growth hormone	Time of feeding	Between-subjects; 3 conditions: ad libitum fed, meal fed for 3 days, meal fed for 14 days	Corticosterone: increase in meal fed compared to ad libitum fed Growth hormone: decrease in meal fed groups compared to ad libitum fed
	Experiment 2	Rats (M)	Corticosterone, growth hormone	Time of feeding	Between-subjects; 2 conditions: ad libitum fed, meal fed for 6 weeks	Corticosterone: increase and growth hormone decrease in the meal fed group
26	Namvar et al., 2016	Rats (M)	Corticosterone	Time of feeding	Between-subjects; 4 conditions: ad libitum fed standard chow, ad libitum high fat, restricted feeding high fat, restricted feeding standard chow	Corticosterone: restricted feeding standard chow: increase in anticipation compared to other conditions Corticosterone: restricted feeding high fat: increase post anticipation compared to other conditions
27	Niijima et al., 1990	Rats (M)	Insulin	Taste of umami and glucose	Between-subjects; 3 conditions: umami taste, glucose taste, NaCl	Insulin: increase in umami and glucose groups
28	Patton et al., 2014	108 rats (M)	Corticosterone, ghrelin	Time of feeding	Between-subjects; 3 conditions: day-fed, night-fed, twice fed	Corticosterone and ghrelin: increase in anticipation of food in day-fed and night-fed rats compared to twice-fed Corticosterone: increase prior to the night meal in twice-fed rats compared to other conditions Ghrelin: increase prior to the day meal in twice-fed rats compared to other conditions
29	Papatryphon et al., 2001	Striped bass	Insulin, glucagon	Food consumption	Between-subjects; 2 conditions: stimulant diet, basal diet	Insulin: increase in stimulant diet group compared to basal diet Glucagon: increase in stimulant diet group compared to basal diet
30	Storlien, 1985 Experiment 1	12 rats	Insulin	Complex stimulus (tone, light, smell) preceding feeding	Between-subjects; 2 conditions: intact, ventromedial hypothalamus area lesion	Insulin: increase in intact condition compared to lesion condition
	Experiment 2	10 rats	Insulin	Complex stimulus (tone, light, smell) preceding feeding	Between-subjects; 2 conditions: intact, vagotomized	Insulin: increase in intact condition compared to vagotomized
31	Strubbe and Steffens, 1975	Rats (M)	Insulin	Food consumption	Within-subjects	Insulin: early increase from baseline at the beginning of feeding
32	Strubbe, 1992	Rats (M)	Insulin	Sound of door opening preceding feeding	Between-subjects; 3 conditions: 2 meals a day, 6 meals a day, ad libitum fed	Insulin: increase in 2 meals a day group compared to other conditions
33	Tonosaki et al., 2007	Rats (F)	Insulin	Sweet solution consumption	Cross-over; 8 conditions: sucrose, acetic acid, salt, quinine, hydrochloride, sodium glutamate, saccharine, starch.	Insulin: increase in saccharine and sucrose conditions compared to other conditions
34	Vahl et al., 2010	Rats (M)	Glucagon-like peptide-1, insulin	Time of feeding		GLP-1: increase in meal fed condition compared to control

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Table 2 (*continued*)

	Authors and year of the paper	N of subjects, specie, sex*	Hormone	Triggering stimulus	Design	Results
					Between-subjects; 2 conditions: meal fed (at certain time), ad libitum control (access to food all the time)	Insulin: increase in meal fed condition compared to control
35	Woods et al., 1977	72 rats	Insulin	Time of feeding	Between-within subjects (time x group), randomized; 2 groups: meal fed (at certain time), ad libitum control (access to food all the time)	Increase in the meal fed group at the feeding time compared to control
36	Bernstein and Woods, 1980	Rats	Insulin	Taste of saccharine	Between-subjects, 4 conditions: total vagotomy, a selective dorsal trunk vagotomy, a selective ventral trunk vagotomy or a sham operation	Increase in insulin in sham operation and a selective ventral trunk vagotomy compared to other conditions

Note. M- male, F- female, * In case no sex is given in the table, it was not available in the original article, n.s.- not significant.

endocrine responses were included in a systematic review published elsewhere (Skvortsova et al., 2019). Studies on anticipatory food responses were selected from the total literature pool and are included in the present review.

2.2. Inclusion criteria

This review included studies on anticipatory food-related hormone release. To be included into the review, the studies had to describe any hormonal response to food related stimuli, such as: feeding time, smell, sight, or any other stimulus related to food. Studies had to include measures of anticipatory hormone release and not hormonal responses to digestion of food. Both animal (including insects) and human studies were included.

2.3. Data search and selection

The data search was performed twice: the first search included all literature from inception until January 2017; the second search included studies from January 2017 until August 2019. The electronic bibliographic databases PubMed, EMBASE, PsycINFO, and CINAHL were searched. The keywords and connectors *endocrine* OR *hormonal* in combination with *conditioning* OR *associative learning* OR *anticipatory release* and specific names of the hormones such as for example *insulin*, *glucagon*, *cortisol* were used (see Appendix A for the full search term). The search was performed by two independent evaluators (A.S., I.K.) and in case of disagreements, a third evaluator (D.S.V.) was consulted. Additional articles were added based on an expert advice.

2.4. Risk of bias assessment

The risk of bias of the included studies was assessed by two authors (A.S. and I.K.). To assess the risk of bias in animal studies, the guidelines from O'Connor and Sargeant (O'Connor and Sargeant, 2014) were used. The Cochrane Collaboration's tool was used for assessing risk of bias in human trials (Higgins et al., 2011). Selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and research personnel), detection bias (blinding of the outcome assessment), attrition bias (incomplete outcome data), and reporting bias (selective reporting) were assessed.

3. Results

3.1. Characteristics of the studies

The literature search yielded in total 19 301 hits after combining both searches and removing duplicates. The number of the articles found on each step of the search is presented in the Appendix B. After subsequent title, abstract and full text check, 89 studies were included in the present review: 36 animal and 53 human studies.

The majority of animal studies were done on males (n = 17) and many studies did not report sex of the animals that were used (n = 14). Only 3 animal studies were done in females and 2 studies in both sexes. 25 out of 36 animal studies were done in rats, 4 studies in dogs, 3 studies in mice, 1 study in wethers and ewes, 1 study in geese, 1 study in drosophila, and 1 study in bass.

Most of human studies included both male and female participants (n = 22) or only male (n = 19). 9 studies were done in females and 3 studies did not report the sex of the participants. Most (n = 33) of the human studies were done in healthy participants. The 18 studies with patients included obese patients (n = 8), patients with anorexia (n = 2), patients with bulimia (n = 2), patients with diabetes type-1 and/or 2 or a family history of diabetes (n = 3), duodenal ulcer patients (n = 1), patients with pancreatic insufficiency (n = 1), and kidney and pancreas transplanted patients (n = 1). An overview of the studies included in this review is presented in the Table 1 (animal studies) and Table 2 (human studies).

The majority of animal and human studies have been evaluated as having an unclear risk of bias (Appendix C) as they were lacking the essential information to evaluate the risk of bias.

3.2. Hormonal outcomes

In animal research, the most commonly measured hormone was insulin that was investigated in 27 studies. Other hormones that were studies in animal research are: corticosterone (n = 4), ghrelin (n = 4), glucagon (n = 3), gastrin (n = 2), glucagon-like peptide-1 (n = 2), motilin (n = 1), pancreatic polypeptide (n = 1), cholecystokinin (n = 1), insulin-like peptides (n = 1), and growth hormone (n = 1).

Human research investigated a wider range of hormones than animal research. Most human studies also focused on insulin (n = 37). Other human studies measured pancreatic polypeptide (n = 13), ghrelin (n = 13), glucagon (n = 7), c-peptide (n = 5), glucagon-like peptide-1 (n = 3), gastrin (n = 3), leptin (n = 3), epinephrine (n = 2), cortisol (n = 2), norepinephrine (n = 2), gastric inhibitory polypeptide (n = 1), obestatin (n = 1), peptide YY (n = 1), anandamide (n = 1), 2-arachidonoyl-glycerol (n = 1), palmitoylethanolamide (n = 1), oleoylethanolamide (n = 1), secretin (n = 1), cholecystokinin (n = 1), and adrenocorticotropic hormone (n = 1).

3.3. Triggering stimulus (i.e. conditioned stimulus)

In order to evaluate the hormonal responses to the food anticipation, several methodological approaches were used. Particularly, studies differed in the choice of the stimuli that were used to trigger the anticipatory food responses.

In animal research, the majority of the studies measured anticipatory hormonal response to a sweet taste (n = 10), time of the day associated with feeding (n = 10), and food consumption in the early stage when the food is not digested yet (n = 9). 2 animal studies employed a sham-feeding procedure: when the subjects are given food to taste and chew and afterwards the food gets expelled and not swallowed. 2 animal studies measured hormonal responses to a sound that was previously

Table 3
Overview of the direction of the results.

Hormone	Triggering stimulus	Proportion of positive results in animal studies	Proportion of positive results in human studies
Insulin	Sweet taste	10/10	5/8
	Food consumption	8/8	4/5
	Sham feeding	–	7/10
	Expectation of food	–	1/2
	Time	3/5	1/1
	Sound	1/1	–
	Food presentation	1/1	6/7
	Expectation of food and sweet taste	–	1/1
	Oral rinsing with glucose	–	0/1
	Complex stimulus	1/1	–
	Pictures of food	–	0/1
	Sham feeding and food consumption	–	0/1
	Discussion about food	0/1	–
Pancreatic polypeptide	Sweet taste	–	0/3
	Sham feeding	1/1	7/8
	Food presentation	–	1/2
Ghrelin	Sweet taste	–	0/1
	Food consumption	–	1/1
	Sham feeding	–	4/4
	Expectation of food	–	2/3
	Time	3/3	2/2
	Food presentation	–	0/1
	Sham feeding and food consumption	–	1/1
Glucagon	Sweet taste	1/1	0/1
	Food consumption	–	1/1
	Sham feeding	–	1/2
	Expectation of food		
	Time	0/1	–
	Sound		
	Food presentation	–	0/1
	Expectation of food and sweet taste		
	Oral rinsing with glucose		
	Complex stimulus		
	Pictures of food	–	0/1
	Sham feeding and food consumption		
	Discussion about food		
C-peptide	Food consumption	–	1/1
	Sham feeding	–	2/3
	Pictures of food	–	0/1
Glucagon-like peptide-1	Expectation of food	–	0/1
	Time	2/2	–
	Food consumption	–	0/1
	Sham feeding	–	0/1
Gastrin	Sham feeding	2/2	2/2
	Discussion about food	–	1/1
Leptin	Expectation of food	–	0/1
	Time	–	0/1
	Food presentation	–	0/1
Cortisol/corticosterone	Expectation of food	–	1/1
	Time	4/4	–
	Sound	–	1/1
Norepinephrine	Sham feeding	–	0/1
	Food presentation	–	0/1
Gastric inhibitory polypeptide	Sound	–	0/1
Obestatin	Sham feeding	–	1/1
Peptide YY	Expectation of food	–	0/1
Anandamide	Expectation of food	–	0/1
2-arachidonoyl-glycerol	Expectation of food	–	0/1
Oleoylethanolamide	Expectation of food	–	0/1
Palmitoylethanolamide	Expectation of food	–	0/1
Secretin	Sham feeding	–	1/1
Cholecystokinin	Sham feeding	0/1	0/1
Adrenocorticotropic hormone	Expectation of food	–	0/1
Motilin	Time	0/1	–
Insulin-like peptides	Smell	1/1	–
Growth hormone	Time	1/1	–

associated with feeding. Single studies used such triggering stimuli as presenting food to the animals without giving them an opportunity to eat it, smell of food, and complex stimulus (combination of smell, light and a sound) previously associated with feeding.

In human research, responses to sham feeding (n = 18) and a sweet non-caloric taste (n = 9) were most commonly measured. Other studies measured anticipatory responses to food consumption before the food gets digested (n = 6), presentation of food (participants were presented with food; they could smell it but were not allowed to consume it; n = 8), expectation of food (participants were told that they would be given food shortly; n = 4), time of the day associated with food consumption (n = 2), combination of food anticipation and a sweet taste (n = 1), oral rinsing with glucose (n = 1), discussion about food (n = 1), presentation of food pictures (n = 1), combination of the presentation of food and imagining eating a favorite meal (n = 1) and sham feeding followed by food consumption(n = 1).

3.4. Findings

The proportion of significant findings per hormonal response and triggering stimulus is presented in Table 3. The majority of the animal studies found anticipatory changes in various hormones, regardless of the study design: 33 out of 36 found a significant anticipatory increase at least in one of the measured hormones. The largest proportion of null findings in animal research (in 4 out of 16 studies) was present in studies that measured hormonal changes in response to the time of day associated with feeding.

Of the human studies, 44 out of 53 of studies found a significant anticipatory increase at least in one of the measured hormones. Insulin

has been investigated most extensively and with highest number of significant results: 24 out of 27 animal and 25 out of 37 human studies found food anticipatory insulin release. The majority of other hormones assessed have also been consistently demonstrated to be triggered by food anticipation with an exception of leptin, gastric inhibitory polypeptide, epinephrine, norepinephrine, palmitoylethanolamide and peptide YY that have been investigated only in a few studies.

The largest evidence for anticipatory insulin release in humans comes from studies that used food consumption (in 4 out of 5 studies significant results were found) and food presentation as triggering stimuli (in 6 out of 7 studies significant results were found). 6 out of 9 studies with sham feeding found anticipatory insulin release. Unlike in animal research that found significant hormone release in response to sweet taste in 100 % of studies, sweet taste was not always successful in eliciting anticipatory hormonal changes in human studies: only 5 out of 8 studies found anticipatory insulin release, and no studies found anticipatory changes in glucagon, pancreatic polypeptide and ghrelin.

Regarding clinical populations, impaired cephalic responses were found in several metabolic and eating disorders in comparison to healthy participants. These impairments have been shown to either enhance cephalic responses, or to completely eliminate them. Enhanced (in comparison to healthy volunteers) cephalic insulin and ghrelin responses were found in anorexia (Broberg and Bernstein, 1989; Monteleone et al., 2008) and bulimia patients (Monteleone et al., 2010). 1 other study did not find differences between bulimia patients and healthy volunteers in cephalic insulin release (Moyer et al., 1993). Contradictory results come from studies in obese participants: 2 studies showed an absence of cephalic responses in obese participants (Brede et al., 2017; Osuna et al., 1986), 2 studies found increased cephalic responses in obese patients in comparison to normal weight participants (Johnson and Wildman, 1983; Sjöström et al., 1980) while 4 other studies did not find difference between obese and healthy volunteers (Parra-Covarrubias et al., 1971; Rigamonti et al., 2015; Simon et al., 1986; Teff et al., 1993a,b). Patients with diabetes and cardiac autonomic neuropathy have been shown to have decreased cephalic pancreatic polypeptide release than diabetic patients without neuropathy and healthy controls (Buysschaert et al., 1985; Glasbrenner et al., 1995). Absence of cephalic secretin release was found in patients with pancreatic insufficiency (Wøjdemann et al., 2000) and absence of cephalic insulin and glucagon release was found in patients with kidney and pancreatic transplant (Secchi et al., 1995). Decreased cephalic pancreatic polypeptide release was found in patients with diabetes type-2 (Glasbrenner et al., 1995).

4. Discussion

There is a large body of research demonstrating that cephalized organisms (ranging from insects to mammals) anticipate food intake via environmental cues with the aim to maintain homeostasis by adjusting their hormonal levels. Anticipatory hormonal changes, so-called cephalic responses, were found in a wide range of hormones but most evidence exists for insulin, ghrelin, pancreatic polypeptide, glucagon, and c-peptide. Animal research is very consistent in finding anticipatory hormonal changes with almost all studies demonstrating significant results, while the majority of human research also finds anticipatory hormonal changes. There is also some evidence for impaired cephalic responses in several metabolic and eating disorders in comparison to healthy participants, although more research is needed. Taken together, the current systematic review shows that the release of a wide range of hormones happens prior to food consumption both in animals and humans and it plays an important role in preparing the organisms for the food ingestion.

The direction of the hormonal changes in response to food anticipation mirrors the hormonal changes in response to food digestion: insulin, ghrelin, glucagon, pancreatic polypeptide, gastrin, and c-peptide levels increase. These processes indicate early adaptive preparation of the organism to the food digestion. The only hormone that does not have a direct relation to metabolism, but was repeatedly investigated in the context of food anticipation, is cortisol (corticosterone in rodents). Cortisol and corticosterone increase were found during food anticipation (Ott et al., 2012) (Coover et al., 1984; Moberg et al., 1975). Moreover, levels of cortisol and corticosterone dropped rapidly after food consumption (Moberg et al., 1975). Speculatively, food anticipation triggers a stress response in the organism and, therefore, leads to cortisol release. Possibly, an increase in stress hormones is necessary to increase alertness in animals in anticipation of food (Feillet, 2010).

It is still not entirely known to what extend cephalic responses are triggered by classical conditioning and whether some of them can be inborn. The only study included in this review that investigated this question directly, (Bernstein and Woods, 1980) demonstrated that cephalic insulin release in response to sweet taste is absent in newborn rat pups but already present in 21−22 day-old rats. Also, multiple experiments in both animals and humans showed that cephalic responses are present in subjects who followed fixed eating pattern in contrast to subjects who were fed ad libitum or without a fixed pattern (Holmes et al., 1989; Moberg et al., 1975; Woods et al., 1977). Therefore, evidence points that cephalic responses are to a large extent dependent on classical conditioning. That is, organisms learn that certain stimuli predict the availability of the food, and respond to these stimuli with cephalic hormones release to prepare the body for food consumption. Cephalic responses have been shown to be elicited not only by the cues that naturalistically predict food (such as time of eating/feeding or smell of food) but also by conditioning to neutral stimuli such as the sound of a door opening (Strubbe, 1992), or a mixed stimulus of a sound and a light (Storlien, 1985).

In addition to memory processes, such innate component, as circadian modulation, seems to affect food anticipatory hormonal responses. One study included in this review investigated a role of circadian clock in the cephalic responses (Patton et al., 2014). Patton and colleagues (2014) demonstrated food anticipatory corticosterone and ghrelin release to be more pronounced in the mice that were fed during the dark phase, than in the mice fed during the light phase. Mice are nocturnal animals, and free fed mice tend to exhibit food anticipatory activity during night. Therefore, the food anticipatory activity seems to be enhanced in the cases when feeding schedule corresponds to the light-dark rhythms. In case when there is a mismatch between dark-light cycle and the feeding pattern, for example, if food is given only in the usual sleep phase, the food anticipatory hormonal responses still appear (Feillet, 2010; Mistlberger, 1994) but might be of a smaller magnitude than in cases when there is no such a mismatch (Patton et al., 2014).

Another not well understood question about the cephalic responses, is what stimuli trigger it and in what cases. There is a discrepancy between animal and human research regarding the question whether mere taste elicits anticipatory hormone release or consumption of whole organoleptic stimulation of foods is needed. A large number of human studies failed to find anticipatory insulin release in response to a sweet taste of a nun-nutritive or low caloric substance alone (Abdallah et al., 1997; Bruce et al., 1987; Cedernaes et al., 2016; Härtel et al., 1993; Morricone et al., 2000; Smeets et al., 2005; Teff et al., 1995). At the same time, the response was found in the large number of studies that used sham feeding with whole foods (Buysschaert et al., 1985; Glasbrenner et al., 1995; Goldschmiedt et al., 1990; Teff et al., 1995, Teff et al., 1993a,b, 1991). Moreover, a number of studies found that there are responders and non-responders to the taste stimulation (Bellisle et al., 1985; Dhillon et al., 2017; Teff et al., 1991). This might indicate that a combination of tactile, olfactory and taste stimulation provided by whole foods is needed to elicit a reliable cephalic response in humans. At the same time, it seems not to be the case in animals. All animal studies included into this review found cephalic hormone release to the sweet taste alone. Various reasons can explain this discrepancy between animal and human research. For example, cognitive factors play an important role in food anticipation in humans. Also, most people have

previous experience with tasting various sweeteners that might affect their cephalic responses, while laboratory animals usually follow standard diets and are naïve to low caloric sweeteners.

Underlying neural mechanisms of the cephalic hormonal responses were investigated only in a few animal and human studies. It is proposed that in response to the food cues, the brain initiates insulin secretion by directing the signal through the vagus nerve to the pancreas (Woods, 1991). Animal research demonstrated that vagotomy, a surgical removal of a part of vagus nerve, leads to the disappearance of cephalic responses (Bernstein and Woods, 1980; Herath et al., 1999; Storlien, 1985). Human research confirms these results: administration of atropine, a drug that opposes the actions of the vagus nerve by blocking the acetylcholine receptors, was shown to abolish cephalic insulin (Sjöström et al., 1980) and pancreatic polypeptide release (Veedfald et al., 2016). Another substrate that has been proposed to underlie cephalic responses is the ventromedial nucleus of the hypothalamus, a brain area that is linked to satiety (Kurrasch et al., 2007). Animals with lesions of this area exhibit no cephalic responses to sweet taste and a complex stimulus previously associated with food (Berthoud et al., 1980a,b; Storlien, 1985). Another human study demonstrated that the upper hypothalamus might play a role in cephalic hormone release but only when stimulated by both sweet taste and high energy content: they showed that the injection of glucose, and not aspartame (sweet non-caloric taste) or maltodextrin (non-sweet carbohydrate) leads to significant decreases in the activity in the upper hypothalamus (Smeets et al., 2005).

Interestingly, human research shows an important role of cognition in food anticipatory hormonal releases. For example, a mere discussion about food triggered insulin release (Feldman and Richardson, 1986) and expected food palatability influenced cephalic responses (Rigamonti et al., 2015). Moreover, Crum and colleagues (Crum et al., 2011) demonstrated that the decrease of ghrelin levels after food consumption was larger in magnitude in participants who thought that they had consumed a high caloric shake in comparison to the participants who thought that the shake was low caloric (in reality it was the same shake). Cognition might also explain the discrepancy in the results between the studies that measured cephalic responses in humans to food consumption and sham feeding. While animal research found that both of these methods are very successful in eliciting anticipatory hormone release, a number of human studies that involved sham feeding, found no such responses. Participants in the studies with sham feeding knew that they would have to discharge the consumed food, and possibly, this knowledge might have affected their anticipatory hormonal responses. These studies point to the importance of conscious expectations in this physiological process: mere thoughts about food that people have might affect their hormonal responses. Additionally, the role of cognitive capacities in food anticipatory responses have never been studied before. For instance, no research in this topic have been done in infants or in people with cognitive disabilities. Future research should look at how cognition about food and cognitive capacities influence learned food anticipatory responses.

Studies that investigated cephalic responses in clinical populations demonstrate that anticipatory hormonal responses were affected in patients with diabetes with cardiac autonomic neuropathy (Buysschaert et al., 1985; Glasbrenner et al., 1995), obesity (Brede et al., 2017; Johnson and Wildman, 1983; Osuna et al., 1986; Sjöström et al., 1980), eating disorders (Broberg and Bernstein, 1989; Monteleone et al., 2010, 2008; Moyer et al., 1993), pancreatic insufficiency (Wøjdemann et al., 2000), and kidney and pancreas transplantation (Secchi et al., 1995). However, the number of studies that included clinical populations is limited. It remains unknown whether disturbed cephalic responses play a causal role in the development of some of these disorders, or, alternatively, are consequences of them. Future studies should investigate the role of cephalic responses in the development of metabolic disorders and the possibility of using cephalic responses as a diagnostic tool for some of these disorders.

Several limitations of the studies included into the current review should be mentioned. First of all, the risk of bias assessment demonstrated that the majority of the studies included in this review did not report enough information to make it possible to objectively assess the bias. Particularly it applies to the animal research that did not provide information regarding the method of assigning animals to different conditions and blinding of the personnel. Similar problems, but to a lesser extent, are present in human studies. Only one study preregistration was available in open access and the majority of the studies did not report whether the analysis of outcome was done by blinded personnel. Moreover, none of the studies described whether the statistical power calculation had been done prior to the study what makes it difficult to interpret null findings. Furthermore, we found that while almost all animal studies found cephalic responses, human research varied more with respect to the results. This phenomenon can be explained by several reasons. Firstly, a larger publication bias might exist in animal research. It has been recently demonstrated that animal studies with null-findings are often not published creating a large bias in the animal literature (ter Riet et al., 2012). Secondly, additional factors might play a role in humans that are presumably less important in animals, for example, cognition. Most of the human studies, however, did not take into considerations such factors, such as expectation of participants, even though cognitive factors have been shown to affect cephalic responses (Crum et al., 2011; Feldman and Richardson, 1986). Ignoring these potential confounding factors, might have led to the occasional null findings in human studies. Most of the animal and human research has been done either in males or in mixed-sex samples. Only one study included in this review looked at sex differences: they demonstrated that anticipatory ghrelin release peaks at different times in male and female mice and also in orchidectomized mice. Sex differences have been also found in glucose and lipid metabolism (Gur et al., 1995), which may potentially also affect anticipatory hormonal responses. Therefore, it is essential that future research focus on potential sex differences in the food anticipatory hormone release. Furthermore, many different methods and protocols were used for measuring anticipatory hormonal responses, and almost no study compared different methods. These differences complicate interpreting null-findings of some of the studies. For example, several studies that involved sham feedings found no cephalic insulin release (Crystal and Teff, 2006; Teff et al., 1995), however, as every study used a different procedure of sham feeding (different foods, various times of chewing, various moments of sample collections), it remains unknown whether these null findings can be explained by the protocol used or whether cephalic insulin release does not occur in all cases.

Better understanding of cephalic hormonal responses brings several clinical possibilities. First, consumption of artificial low-caloric or non-nutritional sweeteners increases in modern society as these sweeteners are often added to common beverages and foods. It is still poorly understood how such discrepancy between the sweet taste and a low nutritional content can affect cephalic responses and whether it plays a role in the development of obesity and metabolic disorders. Moreover, the evidence from the current review indicates that cephalic responses might be affected in patients with metabolic disorders, however, the number of studies on this topic is limited. For example, it is unknown how impairment of cephalic responses progresses from obesity to metabolic syndrome and diabetes type 2. Possibly, measuring cephalic responses might be used as a predictive tool for the development of metabolic disorders.

The present review confirmed that there is a large body of literature supporting the existence of food anticipatory hormonal release. Moreover, there is some preliminary evidence at impairment of anticipatory hormonal responses in a range of disorders related to metabolism and food intake. More research is needed to understand the role of such impairments in cephalic responses and possibility to use cephalic responses as a predictor for the development of metabolic disorders.

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Appendix A. Search terms for the electronic search in PubMed, PsychInfo/CINAHL and Embase

Pubmed	PsychInfo/ CINAHL	Embase
"Hormones"[Mesh] OR "Corticosterone"[Mesh] OR "Hydrocortisone"[Mesh] OR "Adrenocorticotropic Hormone"[Mesh] OR "Corticotropin-Releasing Hormone"[Mesh] OR "Adrenocorticotropic Hormone"[Mesh] OR "Luteinizing Hormone"[Mesh] OR "Testosterone"[Mesh] OR "Estrogens"[Mesh] OR "Gonadotropin-Releasing Hormone"[Mesh] OR "Follicle Stimulating Hormone"[Mesh] OR "Oxytocin"[Mesh] OR "Prolactin"[Mesh] OR "Dehydroepiandrosterone"[Mesh] OR "Progesterone"[Mesh] OR "Thyrotropin-Releasing Hormone"[Mesh] OR "Thyrotropin"[Mesh] OR "Glucagon"[Mesh] OR "Glucagon-Like Peptide 1"[Mesh] OR "Ghrelin"[Mesh] OR "C-Peptide"[Mesh] OR "Insulin"[Mesh] OR "Pancreatic Polypeptide"[Mesh] OR "Leptin"[Mesh] OR "Incretins"[Mesh] OR "Renin"[Mesh] OR "Angiotensins"[Mesh] OR "Aldosterone"[Mesh] OR "Vasopressins"[Mesh] OR "Epinephrine"[Mesh] OR "Norepinephrine"[Mesh] OR "Melatonin"[Mesh] OR "Cholecystokinin"[Mesh] OR "Human Growth Hormone"[Mesh] OR "Insulin-Like Growth Factor I"[Mesh] OR "Melanocyte-Stimulating Hormones"[Mesh] OR "Blood Glucose"[Mesh] OR "Glucose"[Mesh] OR "Glucocorticoids"[Mesh] OR endocrine[Title] OR hormon* [Title] OR neuroendocrine[Title] OR cortisol[Title/Abstract] OR corticosterone[Title/Abstract] OR hydrocortisone[Title/Abstract] OR "adrenocorticotropic hormone"[Title/Abstract] OR adrenocorticotropin[Title/Abstract] OR "corticotropin-releasing hormone"[Title/Abstract] OR estrogen[Title/Abstract] OR testosterone[Title/Abstract] OR "gonadotropin-releasing hormone"[Title/Abstract] OR "luteinizing hormone"[Title/Abstract] OR "follicle-stimulating hormone"[Title/Abstract] OR progesterone[Title/Abstract] OR dehydroepiandrosterone[Title/Abstract] OR oxytocin [Title/Abstract] OR prolactin[Title/Abstract] OR "thyrotropin-releasing hormone"[Title/Abstract] OR "thyroid-stimulating hormone"[Title/Abstract] OR thyrotropin[Title/Abstract] OR glucagon[Title/Abstract] OR "gut peptide*"[Title/Abstract] OR ghrelin[Title/Abstract] OR "glucagon-like peptide"[Title/Abstract] OR insulin[Title/Abstract] OR c-peptide[Title/Abstract] OR "pancreatic polypeptide"[Title/Abstract] OR obestatin[Title/Abstract] OR leptin[Title/Abstract] OR incretin[Title/Abstract] OR renin[Title/Abstract] OR angiotensin[Title/Abstract] OR aldosterone[Title/Abstract] OR "antidiuretic hormone"[Title/Abstract] OR vasopressin[Title/Abstract] OR epinephrine[Title/Abstract] OR adrenaline[Title/Abstract] OR norepinephrine[Title/Abstract] OR noradrenaline[Title/Abstract] OR melatonin[Title/Abstract] OR cholecystokinin[Title/Abstract] OR "growth hormone"[Title/Abstract] OR "insulin-like growth factor 1"[Title/Abstract] OR "melanocyte-stimulating hormone"[Title/Abstract] OR glucose[Title/Abstract] OR "blood sugar"[Title/Abstract] OR glucoregulatory[Title/Abstract] AND "Conditioning (Psychology)"[Mesh] OR "Conditioning, Classical"[Mesh] OR "Association Learning"[Mesh] OR "Anticipation, Psychological"[Mesh] OR "Conditioning (Psychology)"[Mesh] OR Conditioning[Title/Abstract] OR Conditioned[Title/Abstract] OR "Food-anticipatory activity"[Title/Abstract] OR "Meal-anticipatory"[Title/Abstract] OR Anticipatory[Title/Abstract] OR Anticipation [Title/Abstract] OR "Schedule-induced"[Title/Abstract] OR "Cephalic phase"[Title/Abstract] OR "Cephalic insulin"[Title/Abstract] OR "Oral sensory stimulation"[Title/Abstract]	(DE "Classical Conditioning" OR DE "Conditioned Emotional Responses" OR DE "Conditioned Responses" OR DE "Higher Order Conditioning" OR DE "Unconditioned Responses" OR DE "Serial Anticipation (Learning)" OR TI Conditioning OR TI Conditioned OR TI "Food-anticipatory activity" OR TI "Meal-anticipatory" OR TI Anticipatory OR TI Anticipation OR TI "Cephalic phase" OR TI "Cephalic insulin" OR TI "Schedule-induced" OR AB Conditioning OR AB Conditioned OR AB "Food-anticipatory activity" OR AB "Meal-anticipatory" OR AB Anticipatory OR AB Anticipation OR AB "Cephalic phase" OR AB "Cephalic insulin" OR AB "Schedule-induced") AND (DE "Hormones" OR DE "Adrenal Cortex Hormones" OR DE "Adrenal Medulla Hormones" OR DE "Cholecystokinin" OR DE "Corticotropin Releasing Factor" OR DE "Epinephrine" OR DE "Ghrelin" OR DE "Glucagon" OR DE "Gonadotropic Hormones" OR DE "Insulin" OR DE "Leptin" OR DE "Melatonin" OR DE "Orexin" OR DE "Parathyroid Hormone" OR DE "Pituitary Hormones" OR DE "Progestational Hormones" OR DE "Sex Hormones" OR DE "Thyroid Hormones" OR DE "Corticosterone" OR DE "Cortisone" OR DE "Hydrocortisone" OR DE "Corticotropin" OR DE "Estrogens" OR DE "Testosterone" OR DE "Luteinizing Hormone" OR DE "Progesterone" OR DE "Oxytocin" OR DE "Prolactin" OR DE "Thyrotropin" OR DE "Glucagon" OR DE "Ghrelin" OR DE "Insulin" OR DE "Leptin" OR DE "Angiotensin" OR DE "Aldosterone" OR DE "Epinephrine" OR DE "Norepinephrine" OR DE "Melatonin" OR DE "Cholecystokinin" OR DE "Somatropin" OR DE "Vasopressin" OR DE "Melanocyte Stimulating Hormone" OR DE "Glucose" OR DE "Blood Sugar" OR TI "Endocrine" OR TI "Hormon*" OR TI "Neuroendocrine" OR TI "Cortisol" OR TI "Corticosterone" OR TI "Hydrocortisone" OR TI "Adrenocorticotropic hormone" OR TI "Adrenocorticotropin" OR TI "Corticotropin-releasing hormone" OR TI "Estrogen" OR TI "Testosterone" OR TI "Gonadotropin-releasing hormone" OR TI "Luteinizing hormone" OR TI "Follicle-stimulating hormone" OR TI "Progesterone" OR TI "Dehydroepiandrosterone" OR TI "Oxytocin" OR TI "Prolactin" OR TI "Thyrotropin-releasing hormone" OR TI "Thyroid-stimulating hormone "OR TI "Thyrotropin" OR TI "Glucagon" OR TI "Gut peptide*" OR TI "Ghrelin" OR TI "Glucagon-like peptide" OR TI "Insulin" OR TI "C-peptide" OR TI "Pancreatic polypeptide" OR TI "Obestatin" OR TI "Leptin" OR TI "Incretin" OR TI "Renin" OR TI "Angiotensin" OR TI "Aldosterone" OR TI "Antidiuretic hormone" OR TI "Epinephrine" OR TI "Adrenaline" OR TI "Norepinephrine" OR TI "Noradrenaline" OR TI "Melatonin" OR TI "Cholecystokinin" OR TI "Growth hormone" OR TI "Vasopressin" OR TI "Insulin-like growth factor 1" OR TI "Melanocyte-stimulating hormone" OR TI "Glucose" OR TI "Blood sugar" OR TI "Glucoregulatory" OR AB "Endocrine" OR AB "Hormon*" OR AB "Neuroendocrine" OR AB "Cortisol" OR AB "Corticosterone" OR AB "Hydrocortisone" OR AB "Adrenocorticotropic hormone" OR AB "Adrenocorticotropin" OR AB "Corticotropin-releasing hormone" OR AB "Estrogen" OR AB "Testosterone" OR AB "Gonadotropin-releasing hormone" OR AB "Luteinizing hormone" OR AB "Follicle-stimulating hormone" OR AB "Progesterone" OR AB "Dehydroepiandrosterone" OR AB "Oxytocin" OR AB "Prolactin" OR AB "Thyrotropin-releasing hormone" OR AB "Thyroid-stimulating hormone "OR	((endocrine or hormon* or neuroendocrine or cortisol or corticosterone or hydrocortisone or adrenocorticotropic hormone or adrenocorticotropin or corticotropin-releasing hormone or estrogen or testosterone or gonadotropin-releasing hormone or luteinizing hormone or follicle-stimulating hormone or progesterone or dehydroepiandrosterone or oxytocin or prolactin or thyrotropin-releasing hormone or thyroid-stimulating hormone or thyrotropin or glucagon or gut peptide* or ghrelin or glucagon-like peptide or insulin or c-peptide or pancreatic polypeptide or obestatin or leptin or incretin or renin or angiotensin or aldosterone or antidiuretic hormone or vasopressin or epinephrine or adrenaline or norepinephrine or noradrenaline or melatonin or cholecystokinin or growth hormone or insulin-like growth factor 1 or melanocyte-stimulating hormone or glucose or blood sugar or glucoregulatory).ti. or (cortisol or corticosterone or hydrocortisone or adrenocorticotropic hormone or adrenocorticotropin or corticotropin-releasing hormone or estrogen or testosterone or gonadotropin-releasing hormone or luteinizing hormone or follicle-stimulating hormone or progesterone or dehydroepiandrosterone or oxytocin or prolactin or thyrotropin-releasing hormone or thyroid-stimulating hormone or thyrotropin or glucagon or gut peptide* or ghrelin or glucagon-like peptide or insulin or c-peptide or pancreatic polypeptide or obestatin or leptin or incretin or renin or angiotensin or aldosterone or antidiuretic hormone or vasopressin or epinephrine or adrenaline or norepinephrine or noradrenaline or melatonin or cholecystokinin or growth hormone or insulin-like growth factor 1 or melanocyte-stimulating hormone or glucose or blood sugar or glucoregulatory).ab.) AND ((Conditioning or Conditioned or Food-anticipatory activity or Meal-anticipatory or Anticipatory or Anticipation or Schedule-induced or Cephalic phase or Cephalic insulin or Oral sensory stimulation).ti. or (Conditioning or Conditioned or Food-anticipatory activity or Meal-anticipatory or Anticipatory or Anticipation or Schedule-induced or Cephalic phase or Cephalic insulin or Oral sensory stimulation).ab.)

(*continued on next page*)

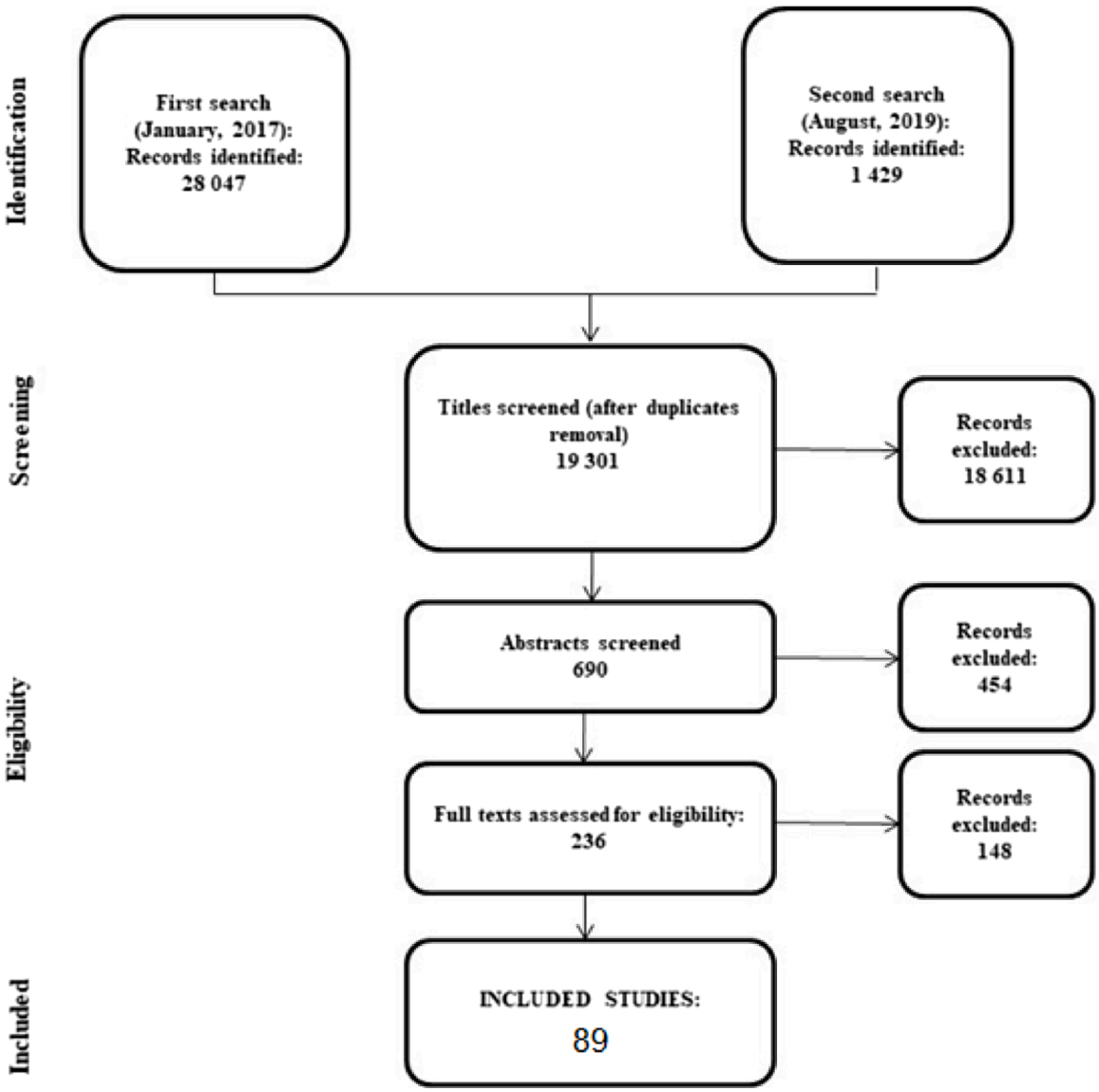


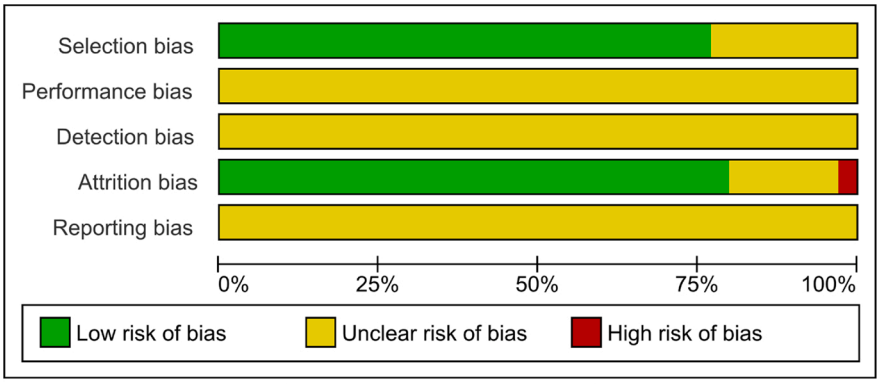
Fig. A1. Flow diagram with the number of included and excluded studies.

(*continued*)

Pubmed	PsychInfo/ CINAHL	Embase
	AB "Thyrotropin" OR AB "Glucagon" OR AB "Gut peptide*" OR AB "Ghrelin" OR AB "Glucagon-like peptide" OR AB "Insulin" OR AB "C-peptide" OR AB "PancreaABc polypeptide" OR AB "Obestatin" OR AB "Leptin" OR AB "Incretin" OR AB "Renin" OR AB "Angiotensin" OR AB "Aldosterone" OR AB "Antidiuretic hormone" OR AB "Epinephrine" OR AB "Adrenaline" OR AB "Norepinephrine" OR AB "Noradrenaline" OR AB "Melatonin" OR AB "Cholecystokinin" OR AB "Growth hormone" OR AB "Vasopressin" OR AB "Insulin-like growth factor 1" OR AB "Melanocyte-stimulating hormone" OR AB "Glucose" OR AB "Blood sugar" OR AB "Glucoregulatory")	

Appendix B

see Figs. A1–A3



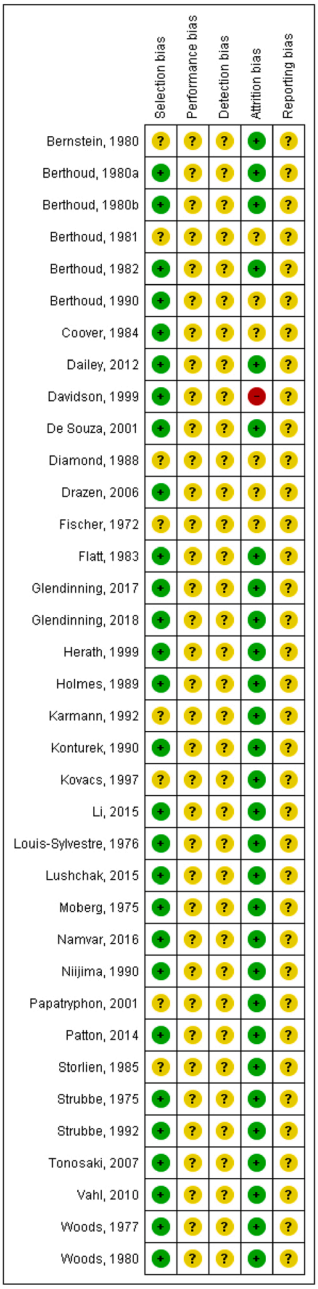


Fig. A2. Risk of bias for animal studies. Risk of bias is presented as a percentage across all included studies and for each separate study.

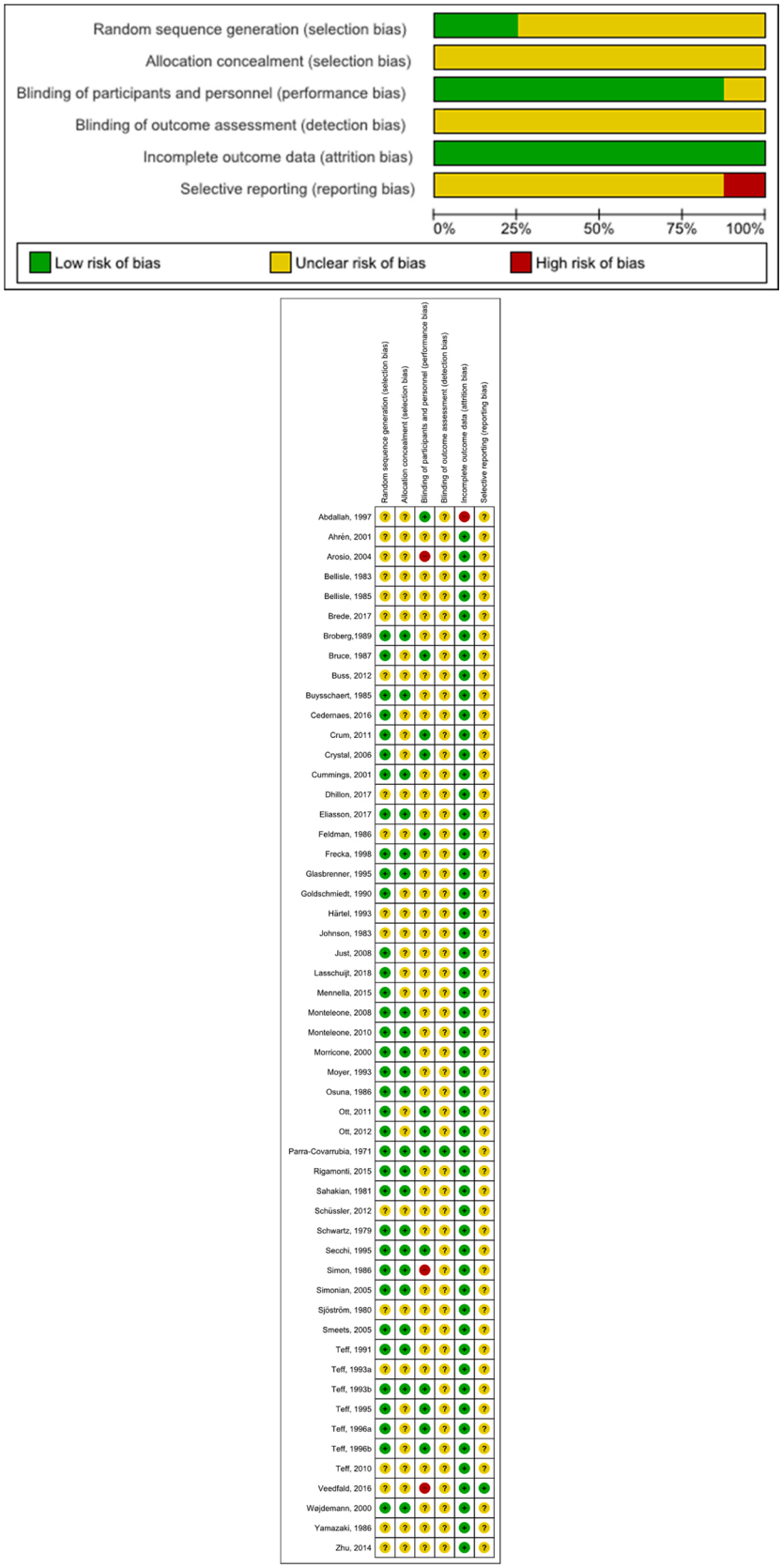


Fig. A3. Risk of bias for human studies. Risk of bias is presented as a percentage across all included studies and for each separate study.

References

Abdallah, L., Chabert, M., Louis-Sylvestre, J., 1997. Cephalic phase responses to sweet taste. Am. J. Clin. Nutr. 65, 737–743. https://doi.org/10.1093/ajcn/65.3.737.

Ahrén, B., Holst, J.J., 2001. The cephalic insulin response to meal ingestion in humans is dependent on both cholinergic and noncholinergic mechanisms and is important for postprandial glycemia. Diabetes 50, 1030–1038.

Arosio, M., Ronchi, C.L., Beck-Peccoz, P., Gebbia, C., Giavoli, C., Cappiello, V., Conte, D., Peracchi, M., 2004. Effects of modified sham feeding on ghrelin levels in healthy human subjects. J. Clin. Endocrinol. Metab. 89, 5101–5104.

Aschoff, J., 1991. Activity in anticipation and in succession of a daily meal. Boll. Della Soc. Ital. Biol. Sper. 67, 213–228.

Bellisle, F., Louis-Sylvestre, J., Demozay, F., Blazy, D., Le Magnen, J., 1983. Reflex insulin response associated to food intake in human subjects. Physiol. Behav. 31, 515–521.

Bellisle, F., Louis-Sylvestre, J., Demozay, F., Blazy, D., Le Magnen, J., 1985. Cephalic phase of insulin secretion and food stimulation in humans: a new perspective. Am. J. Physiol. Endocrinol. Metab. 249, E639–E645.

Bernstein, I.L., Woods, S.C., 1980. Ontogeny of cephalic insulin release by the rat. Physiol. Behav. 24, 529–532.

Berthoud, H.R., Jeanrenaud, B., 1982. Sham feeding-induced cephalic phase insulin release in the rat. Am. J. Physiol. Endocrinol. Metab. 242, E280–E285.

Berthoud, H.-R., Powley, T.L., 1990. Identification of vagal preganglionics that mediate cephalic phase insulin response. Am. J. Physiol. Regul. Integr. Comp. Physiol. 258, R523–R530.

Berthoud, H.R., Bereiter, D.A., Jeanrenaud, B., 1980a. VMH procainization abolishes cephalic phase insulin response. Brain Res. Bull. 5, 127–131.

Berthoud, H.R., Trimble, E.R., Siegel, E.G., Bereiter, D.A., Jeanrenaud, B., 1980b. Cephalic-phase insulin secretion in normal and pancreatic islet-transplanted rats. Am. J. Physiol. Endocrinol. Metab. 238, E336–E340.

Berthoud, H.R., Bereiter, D.A., Trimble, E.R., Siegel, E.G., Jeanrenaud, B., 1981. Cephalic phase, reflex insulin secretion neuroanatomical and physiological characterization. Diabetologia 20, 393–401.

Brede, S., Sputh, A., Hartmann, A.-C., Hallschmid, M., Lehnert, H., Klement, J., 2017. Visual food cues decrease postprandial glucose concentrations in lean and obese men without affecting food intake and related endocrine parameters. Appetite 117, 255–262. https://doi.org/10.1016/j.appet.2017.07.001.

Broberg, D.J., Bernstein, I.L., 1989. Cephalic insulin release in anorexic women. Physiol. Behav. 45, 871–874.

Bruce, D.G., Storlien, L.H., Furler, S.M., Chisholm, D.J., 1987. Cephalic phase metabolic responses in normal weight adults. Metabolism 36, 721–725.

Buss, C., Kraemer-Aguiar, L.G., Maranhão, P.A., Marinho, C., Maria das Graças, C., Wiernsperger, N., Bouskela, E., 2012. Novel findings in the cephalic phase of digestion: a role for microcirculation? Physiol. Behav. 105, 1082–1087.

Buysschaert, M., Donckier, J., Dive, A., Ketelslegers, J.-M., Lambert, A.E., 1985. Gastric acid and pancreatic polypeptide responses to sham feeding are impaired in diabetic subjects with autonomic neuropathy. Diabetes 34, 1181–1185.

Cedernaes, J., Lampola, L., Axelsson, E.K., Liethof, L., Hassanzadeh, S., Yeganeh, A., Broman, J.-E., Schiöth, H.B., Benedict, C., 2016. A single night of partial sleep loss impairs fasting insulin sensitivity but does not affect cephalic phase insulin release in young men. J. Sleep Res. 25, 5–10.

Colette, C., Monnier, L., 2007. Acute glucose fluctuations and chronic sustained hyperglycemia as risk factors for cardiovascular diseases in patients with type 2 diabetes. Horm. Metab. Res. 39, 683–686.

Coover, G.D., Murison, R., Sundberg, H., Jellestad, F., Ursin, H., 1984. Plasma corticosterone and meal expectancy in rats: effects of low probability cues. Physiol. Behav. 33, 179–184.

Crum, A.J., Corbin, W.R., Brownell, K.D., Salovey, P., 2011. Mind over milkshakes: mindsets, not just nutrients, determine ghrelin response. Health Psychol. 30, 424.

Crystal, S.R., Teff, K.L., 2006. Tasting fat: cephalic phase hormonal responses and food intake in restrained and unrestrained eaters. Physiol. Behav. 89, 213–220.

Cummings, D.E., Purnell, J.Q., Frayo, R.S., Schmidova, K., Wisse, B.E., Weigle, D.S., 2001. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 50, 1714–1719.

Dailey, M.J., Stingl, K.C., Moran, T.H., 2012. Disassociation between preprandial gut peptide release and food-anticipatory activity. Endocrinology 153, 132–142.

Davidson, A.J., Stephan, F.K., 1999. Plasma glucagon, glucose, insulin, and motilin in rats anticipating daily meals. Physiol. Behav. 66, 309–315.

De Souza, C.J., Russo, P., Lozito, R., Dunning, B.E., 2001. Differential effects of short and long duration insulinotropic agents on meal-related glucose excursions. Diabetes Obes. Metab. 3, 73–83.

Dhillon, J., Lee, J.Y., Mattes, R.D., 2017. The cephalic phase insulin response to nutritive and low-calorie sweeteners in solid and beverage form. Physiol. Behav. 181, 100–109. https://doi.org/10.1016/j.physbeh.2017.09.009.

Diamond, P., LeBlanc, J., 1988. A role for insulin in cephalic phase of postprandial thermogenesis in dogs. Am. J. Physiol. Endocrinol. Metab. 254, E625–E632.

Drazen, D.L., Vahl, T.P., D'Alessio, D.A., Seeley, R.J., Woods, S.C., 2006. Effects of a fixed meal pattern on ghrelin secretion: evidence for a learned response independent of nutrient status. Endocrinology 147, 23–30.

Eliasson, B., Rawshani, A., Axelsen, M., Hammarstedt, A., Smith, U., 2017. Cephalic phase of insulin secretion in response to a meal is unrelated to family history of type 2 diabetes. PLoS One 12, e0173654. https://doi.org/10.1371/journal.pone.0173654.

Feillet, C.A., 2010. Food for thoughts: feeding time and hormonal secretion. J. Neuroendocrinol. 22, 620–628.

Feldman, M., Richardson, C.T., 1986. Role of thought, sight, smell, and taste of food in the cephalic phase of gastric acid secretion in humans. Gastroenterology 90, 428–433.

Fischer, U., Hommel, H., Ziegler, M., Michael, R., 1972. The mechanism of insulin secretion after oral glucose administration. Diabetologia 8, 104–110.

Flatt, P.R., Bailey, C.J., 1983. Glucose and insulin response to conditioned feeding in lean and genetically obese hyperglycemic (obob) mice. Metabolism 32, 504–509.

Frecka, J.M., Mattes, R.D., 2008. Possible entrainment of ghrelin to habitual meal patterns in humans. Am. J. Physiol. Gastrointest. Liver Physiol. 294, G699–G707.

Giduck, S.A., Threatte, R.M., Kare, M.R., 1987. Cephalic reflexes: their role in digestion and possible roles in absorption and metabolism. J. Nutr. 117, 1191–1196.

Glasbrenner, B., Brückel, J., Gritzmann, R., Adler, G., 1995. Cephalic phase of pancreatic polypeptide release: a valid test of autonomic neuropathy in diabetics? Diabetes Res. Clin. Pract. 30, 117–123.

Glendinning, J.I., Frim, Y.G., Hochman, A., Lubitz, G.S., Basile, A.J., Sclafani, A., 2017. Glucose elicits cephalic-phase insulin release in mice by activating KATP channels in taste cells. Am. J. Physiol. Regul. Integr. Comp. Physiol. 312, R597–R610. https://doi.org/10.1152/ajpregu.00433.2016.

Glendinning, J.I., Lubitz, G.S., Shelling, S., 2018. Taste of glucose elicits cephalic-phase insulin release in mice. Physiol. Behav. 192, 200–205. https://doi.org/10.1016/j.physbeh.2018.04.002.

Goldschmiedt, M., Redfern, J.S., Feldman, M., 1990. Food coloring and monosodium glutamate: effects on the cephalic phase of gastric acid secretion and gastrin release in humans. Am. J. Clin. Nutr. 51, 794–797.

Gur, R.C., Mozley, L.H., Mozley, P.D., Resnick, S.M., Karp, J.S., Alavi, A., Arnold, S.E., Gur, R.E., 1995. Sex differences in regional cerebral glucose metabolism during a resting state. Science 267, 528–531.

Hadamitzky, M., Lückemann, L., Pacheco-López, G., Schedlowski, M., 2019. Pavlovian conditioning of immunological and neuroendocrine functions. Physiol. Rev. 100, 357–405.

Härtel, B., Graubaum, H., Schneider, B., 1993. The influence of sweetener solutions on the secretion of insulin and the blood glucose level. Ernhrungsumschau 40, 152–155.

Herath, C.B., Reynolds, G.W., Mackenzie, D.D.S., Davis, S.R., Harris, P.M., 1999. Vagotomy suppresses cephalic phase insulin release in sheep. Exp. Physiol. 84, 559–569.

Holmes, L.J., Smythe, G.A., Storlien, L.H., 1989. Monoaminergic activity at the level of the hypothalamus and striatum: relationship to anticipated feeding and pancreatic insulin responses. Brain Res. 496, 204–210.

Johnson, W.G., Wildman, H.E., 1983. Influence of external and covert food stimuli on insulin secretion in obese and normal persons. Behav. Neurosci. 97, 1025.

Just, T., Pau, H.W., Engel, U., Hummel, T., 2008. Cephalic phase insulin release in healthy humans after taste stimulation? Appetite 51, 622–627.

Karmann, H., Rideau, N., Zorn, T., Malan, A., Le Maho, Y., 1992. Early insulin response after food intake in geese. Am. J. Physiol. Regul. Integr. Comp. Physiol. 263, R782–R784.

Konturek, S.J., Bielanski, W., Solomon, T.E., 1990. Effects of an antral mucosectomy, L-364,718 and atropine on cephalic phase of gastric and pancreatic secretion in dogs. Gastroenterology 98, 47–55.

Kovacs, T.O., Lloyd, K.C., Lawson, D.C., Pappas, T.N., Walsh, J.H., 1997. Inhibition of sham feeding-stimulated acid secretion in dogs by immunoneutralization of gastrin. Am. J. Physiol. Gastrointest. Liver Physiol. 273, G399–G403.

Kurrasch, D.M., Cheung, C.C., Lee, F.Y., Tran, P.V., Hata, K., Ingraham, H.A., 2007. The neonatal ventromedial hypothalamus transcriptome reveals novel markers with spatially distinct patterning. J. Neurosci. 27, 13624–13634.

Lasschuijt, M.P., Mars, M., de Graaf, C., Smeets, P.A., 2020. Endocrine cephalic phase responses to food cues: a systematic review. Adv. Nutr.

Li, Z., Wang, Y., Sun, K.K., Wang, K., Sun, Z.S., Zhao, M., Wang, J., 2015. Sex-related difference in food-anticipatory activity of mice. Horm. Behav. 70, 38–46.

Louis-Sylvestre, J., 1976. Preabsorptive insulin release and hypoglycemia in rats. Am. J. Physiol. Leg. Content 230, 56–60.

Lushchak, V., Carlsson, M.A., Nässel, D.R., 2015. Food odors trigger an endocrine response that affects food ingestion and metabolism. Cell. Mol. Life Sci. 72, 3143–3155.

Mennella, I., Ferracane, R., Zucco, F., Fogliano, V., Vitaglione, P., 2015. Food liking enhances the plasma response of 2-arachidonoylglycerol and of pancreatic polypeptide upon modified sham feeding in humans. J. Nutr. 145, 2169–2175.

Mistlberger, R.E., 1994. Circadian food-anticipatory activity: formal models and physiological mechanisms. Neurosci. Biobehav. Rev. 18, 171–195.

Moberg, G.P., Bellinger, L.L., Mendel, V.E., 1975. Effect of meal feeding on daily rhythms of plasma corticosterone and growth hormone in the rat. Neuroendocrinology 19, 160–169.

Monteleone, P., Serritella, C., Martiadis, V., Maj, M., 2008. Deranged secretion of ghrelin and obestatin in the cephalic phase of vagal stimulation in women with anorexia nervosa. Biol. Psychiatry 64, 1005–1008.

Monteleone, P., Serritella, C., Scognamiglio, P., Maj, M., 2010. Enhanced ghrelin secretion in the cephalic phase of food ingestion in women with bulimia nervosa. Psychoneuroendocrinology 35, 284–288. https://doi.org/10.1016/j.psyneuen.2009.07.001.

Morricone, L., Bombonato, M., Cattaneo, A.G., Enrini, R., Lugari, R., Zandomenighi, R., Caviezel, F., 2000. Food-related sensory stimuli are able to promote pancreatic polypeptide elevation without evident cephalic phase insulin secretion in human obesity. Horm. Metab. Res. 32, 240–245.

Moyer, A., Rodin, J., Cummings, N., 1993. Cephalic phase insulin release in bulimia. Int. J. Eat. Disord. 14, 331–339.

Namvar, S., Gyte, A., Denn, M., Leighton, B., Piggins, H.D., 2016. Dietary fat and corticosterone levels are contributing factors to meal anticipation. Am. J. Physiol. Regul. Integr. Comp. Physiol. 310, R711–R723.
Niijima, A., Togiyama, T., Adachi, A., 1990. Cephalic-phase insulin release induced by taste stimulus of monosodium glutamate (umami taste). Physiol. Behav. 48, 905–908.
O'Connor, A.M., Sargeant, J.M., 2014. Critical appraisal of studies using laboratory animal models. ILAR J. 55, 405–417.
Osuna, J.I., Pages, I., Motino, M.A., Rodriguez, E., Osorio, C., 1986. Cephalic phase of insulin secretion in obese women. Horm. Metab. Res. 18, 473–475.
Ott, V., Friedrich, M., Prilop, S., Lehnert, H., Jauch-Chara, K., Born, J., Hallschmid, M., 2011. Food anticipation and subsequent food withdrawal increase serum cortisol in healthy men. Physiol. Behav. 103, 594–599.
Ott, V., Friedrich, M., Zemlin, J., Lehnert, H., Schultes, B., Born, J., Hallschmid, M., 2012. Meal anticipation potentiates postprandial ghrelin suppression in humans. Psychoneuroendocrinology 37, 1096–1100.
Papatryphon, E., Capilla, E., Navarro, I., Soares, J.H., 2001. Early insulin and glucagon response associated with food intake in a teleost, the striped bass (Morone saxatilis). Fish Physiol. Biochem. 24, 31–39.
Parra-Covarrubias, A., Rivera-Rodriguez, I., Almaraz-Ugalde, A., 1971. Cephalic phase of insulin secretion in obese adolescents. Diabetes 20, 800–802.
Patton, D.F., Katsuyama, A.M., Pavlovski, I., Michalik, M., Patterson, Z., Parfyonov, M., Smit, A.N., Marchant, E.G., Chung, J., Abizaid, A., 2014. Circadian mechanisms of food anticipatory rhythms in rats fed once or twice daily: clock gene and endocrine correlates. PLoS One 9.
Pavlov, I.P., 1902. The Work of the Digestive Glands. Charles Griffin and Co., Ltd., London.
Pavlov, I.P., 1927. Conditional Reflexes: an Investigation of the Physiological Activity of the Cerebral Cortex.
Power, M.L., Schulkin, J., 2008. Anticipatory physiological regulation in feeding biology: cephalic phase responses. Appetite 50, 194–206.
Pozo, M., Claret, M., 2018. Hypothalamic control of systemic glucose homeostasis: the pancreas connection. Trends Endocrinol. Metab. 29, 581–594. https://doi.org/10.1016/j.tem.2018.05.001.
Rigamonti, A.E., Piscitelli, F., Aveta, T., Agosti, F., De Col, A., Bini, S., Cella, S.G., Di Marzo, V., Sartorio, A., 2015. Anticipatory and consummatory effects of (hedonic) chocolate intake are associated with increased circulating levels of the orexigenic peptide ghrelin and endocannabinoids in obese adults. Food Nutr. Res. 59, 29678.
Ryu, T.Y., Park, J., Scherer, P.E., 2014. Hyperglycemia as a risk factor for cancer progression. Diabetes Metab. J. 38, 330–336. https://doi.org/10.4093/dmj.2014.38.5.330.
Sahakian, B.J., Lean, M.E.J., Robbins, T.W., James, W.P.T., 1981. Salivation and insulin secretion in response to food in non-obese men and women. Appetite 2, 209–216.
Schulkin, J., 2003. Rethinking Homeostasis: Allostatic Regulation in Physiology and Pathophysiology. MIT Press.
Schulkin, J., 2011. Social allostasis: anticipatory regulation of the internal milieu. Front. Evol. Neurosci. 2, 111.
Schüssler, P., Kluge, M., Yassouridis, A., Dresler, M., Uhr, M., Steiger, A., 2012. Ghrelin levels increase after pictures showing food. Obesity 20, 1212–1217.
Schwartz, T.W., Stenquist, B., Olbe, L., 1979. Cephalic phase of pancreatic-polypeptide secretion studied by sham feeding in man. Scand. J. Gastroenterol. 14, 313–320.
Secchi, A., Caldara, R., Caumo, A., Monti, L.D., Bonfatti, D., Di Carlo, V., Pozza, G., 1995. Cephalic-phase insulin and glucagon release in normal subjects and in patients receiving pancreas transplantation. Metabolism 44, 1153–1158.
Simon, C., Schlienger, J.L., Sapin, R., Imler, M., 1986. Cephalic phase insulin secretion in relation to food presentation in normal and overweight subjects. Physiol. Behav. 36, 465–469.
Simonian, H.P., Kresge, K.M., Boden, G.H., Parkman, H.P., 2005. Differential effects of sham feeding and meal ingestion on ghrelin and pancreatic polypeptide levels: evidence for vagal efferent stimulation mediating ghrelin release. Neurogastroenterol. Motil. Off. J. Eur. Gastrointest. Motil. Soc. 17, 348–354. https://doi.org/10.1111/j.1365-2982.2004.00634.x.
Sjöström, L., Garellick, G., Krotkiewski, M., Luyckx, A., 1980. Peripheral insulin in response to the sight and smell of food. Metab. Clin. Exp. 29, 901–909.
Skvortsova, A., Veldhuijzen, D.S., Kloosterman, I.E.M., Meijer, O.C., van Middendorp, H., Pacheco-Lopez, G., Evers, A.W.M., 2019. Conditioned hormonal responses: a systematic review in animals and humans. Front. Neuroendocrinol. 52, 206–218. https://doi.org/10.1016/j.yfrne.2018.12.005.
Smeets, P.A., de Graaf, C., Stafleu, A., van Osch, M.J., van der Grond, J., 2005. Functional magnetic resonance imaging of human hypothalamic responses to sweet taste and calories. Am. J. Clin. Nutr. 82, 1011–1016.
Smeets, P.A., Erkner, A., De Graaf, C., 2010. Cephalic phase responses and appetite. Nutr. Rev. 68, 643–655.
Storlien, L.H., 1985. The ventromedial hypothalamic area and the vagus are neural substrates for anticipatory insulin release. J. Auton. Nerv. Syst. 13, 303–310.
Strubbe, J.H., 1992. Parasympathetic involvement in rapid meal-associated conditioned insulin secretion in the rat. Am. J. Physiol. Regul. Integr. Comp. Physiol. 263, R615–R618.
Strubbe, J.H., Steffens, A.B., 1975. Rapid insulin release after ingestion of a meal in the unanesthetized rat. Am. J. Physiol. Leg. Content 229, 1019–1022.
Teff, K.L., 2010. Cephalic phase pancreatic polypeptide responses to liquid and solid stimuli in humans. Physiol. Behav. 99, 317–323.
Teff, K.L., 2011. How neural mediation of anticipatory and compensatory insulin release helps us tolerate food. Physiol. Behav. 103, 44–50.
Teff, K.L., Engelman, K., 1996a. Palatability and dietary restraint: effect on cephalic phase insulin release in women. Physiol. Behav. 60, 567–573.
Teff, K.L., Engelman, K., 1996b. Oral sensory stimulation improves glucose tolerance in humans: effects on insulin, C-peptide, and glucagon. Am. J. Physiol. Regul. Integr. Comp. Physiol. 270, R1371–R1379.
Teff, K.L., Mattes, R.D., Engelman, K., 1991. Cephalic phase insulin release in normal weight males: verification and reliability. Am. J. Physiol. 261, E430–436. https://doi.org/10.1152/ajpendo.1991.261.4.E430.
Teff, K.L., Levin, B.E., Engelman, K., 1993a. Oral sensory stimulation in men: effects on insulin, C-peptide, and catecholamines. Am. J. Physiol. Regul. Integr. Comp. Physiol. 265, R1223–R1230.
Teff, K.L., Mattes, R.D., Engelman, K., Mattern, J., 1993b. Cephalic-phase insulin in obese and normal-weight men: relation to postprandial insulin. Metabolism 42, 1600–1608.
Teff, K.L., Devine, J., Engelman, K., 1995. Sweet taste: effect on cephalic phase insulin release in men. Physiol. Behav. 57, 1089–1095.
ter Riet, G., Korevaar, D.A., Leenaars, M., Sterk, P.J., Van Noorden, C.J., Bouter, L.M., Lutter, R., Elferink, R.P.O., Hooft, L., 2012. Publication bias in laboratory animal research: a survey on magnitude, drivers, consequences and potential solutions. PLoS One 7, e43404.
Tonosaki, Kazuyuki, Hori, Y., Shimizu, Y., Tonosaki, Keiichi, 2007. Relationships between insulin release and taste. Biomed. Res. 28, 79–83.
Vahl, T.P., Drazen, D.L., Seeley, R.J., D'Alessio, D.A., Woods, S.C., 2010. Meal-anticipatory glucagon-like peptide-1 secretion in rats. Endocrinology 151, 569–575.
Veedfald, S., Plamboeck, A., Deacon, C.F., Hartmann, B., Knop, F.K., Vilsbøll, T., Holst, J. J., 2016. Cephalic phase secretion of insulin and other enteropancreatic hormones in humans. Am. J. Physiol. Gastrointest. Liver Physiol. 310, G43–G51.
Wiedemann, S.J., Rachid, L., Illigens, B., Böni-Schnetzler, M., Donath, M.Y., 2020. Evidence for cephalic phase insulin release in humans: a systematic review and meta-analysis. Appetite, 104792.
Wøjdemann, M., Sternby, B., Larsen, S., Olsen, O., 2000. Cephalic phase of lipolysis is impaired in pancreatic insufficiency: role of gastric lipase. Scand. J. Gastroenterol. 35, 204–211.
Woods, S.C., 1991. The eating paradox: how we tolerate food. Psychol. Rev. 98, 488.
Woods, S.C., 2002. The house economist and the eating paradox. Appetite 38, 161–165.
Woods, S.C., Vasselli, J.R., Kaestner, E., Szakmary, G.A., Milburn, P., Vitiello, M.V., 1977. Conditioned insulin secretion and meal feeding in rats. J. Comp. Physiol. Psychol. 91, 128.
Yamashita, H., Iwai, M., Nishimura, K., Kobayashi, N., Shimazu, T., 1993. Altered lipid metabolism during enteral or parenteral nutrition in rats: comparison with oral feeding. J. Nutr. Sci. Vitaminol. 39, 151–161.
Yamazaki, M., Sakaguchi, T., 1986. Effects of D-glucose anomers on sweetness taste and insulin release in man. Brain Res. Bull. 17, 271–274.
Yeomans, M.R., 2006. Olfactory influences on appetite and satiety in humans. Physiol. Behav. 87, 800–804.
Zafra, M.A., Molina, F., Puerto, A., 2006. The neural/cephalic phase reflexes in the physiology of nutrition. Neurosci. Biobehav. Rev. 30, 1032–1044.
Zhu, Y., Hsu, W.H., Hollis, J.H., 2014. Modified sham feeding of foods with different macronutrient compositions differentially influences cephalic change of insulin, ghrelin, and NMR-based metabolomic profiles. Physiol. Behav. 135, 135–142.