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

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A B S T R A C T

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 allostatics: “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...
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 changes 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 (Pozzo and Claret, 2018), and 2) via the brain-stem 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 rhythm:
### 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-polypeptide, unsweetened polypeptide | Insulin: n.s. in all conditions Glucagon: n.s. in all conditions |
| 2 Ahren 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: taste 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 Pancreatic polypeptide: increase in healthy controls and patients without cardiac autonomic neuropathy compared to diabetes patients with cardiac autonomic neuropathy |
| 10 Buyschaert et al., 1985 | 16 (8 M, 8 F)     | Pancreatic polypeptide         | Sham feeding                            | Between-subjects, 3 groups: healthy controls, diabetes patients with cardiac autonomic neuropathy, diabetes patients without cardiac autonomic neuropathy | Insulin: n.s. in both groups |
| 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. |
| 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. Insulin: increase in sucrose and sucralose conditions from baseline. Solid form higher than liquid form. |
| 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 both groups from baseline C-peptide: increase in both groups from baseline |
| 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 (continued on next page) |
| First author and year       | Sample size (sex*) | Hormones (Conditioned Response) | Triggering stimulus (Conditioned Stimulus) | Experimental design | Results                                                                                                                                 |
|-----------------------------|--------------------|---------------------------------|--------------------------------------------|---------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| 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 Härte l 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 healthy controls                                                                                   |
| 28 Morricone et al., 2000  | 12 (3 M, 9 F)      | Pancreatic polypeptide, insulin | Sweet taste                                | Cross-over; 3 conditions: oral rine with saccharine, lemon juice, water | Pancreatic polypeptide: n.s. Insulin: n.s.                                                                                                                                                         |
| Experiment 1                |                    |                                 |                                            | Cross-over; 3 conditions: sight and smell, sight only, smell only |                                                                                                                                                                                                |
| Experiment 2                |                    |                                 |                                            | Pancreatic polypeptide, insulin |                                                                                                                                                                                                |
| 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 | Pancreatic polypeptide: increase in all conditions from baseline Insulin: n.s. Epinephrine: n.s. Norepinephrine: n.s.                                                                                                                                 |
| 29 Osuna et al., 1986       | 15 (F)             | Insulin                         | Presentation of food                       | Insulin: increase during 2nd presentation in both groups compared to the first presentation | Insulin: increase in healthy controls compared to obese patients (continued on next page)                                                                                                          |
| First author and year | Sample size (sex*) | Hormones (Conditioned Response) | Triggering stimulus (Conditioned Stimulus) | Experimental design | Results |
|-----------------------|--------------------|----------------------------------|--------------------------------------------|--------------------|---------|
| A. Skvortsova et al.  |                    |                                  |                                            |                    |         |
| 43 Sahakian et al., 1981 | 14 (10 M, 4 F)     | Insulin, glucagon                | Presentation of palatable food              | Within-subjects    |         |
| 44 Simon et al., 1986 | 25 (12 M, 13 F)    | Insulin                          | Presentation of food                        | Between-subjects    |         |
| 45 Simonian et al., 2005 | 15 (6 M, 9 F)     | Pancreatic polypeptide, ghrelin, insulin | Sham feeding followed by food consumption | Within-subjects    |         |
| 46 Sjostrom 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 |         |
| 47 Teff et al., 1991 | 20 (M)             | Insulin                          | Sham feeding                               | Within-subjects; 3 trials |         |
| 48 Teff et al., 1996b | 13 (F)             | Insulin                          | Sham feeding                               | Cross-over; 2 conditions: palatable, non-palatable food |         |
| 49 Teff and Engelman, 1999a | 10 (M)            | Ghrelin, pancreatic polypeptide, leptin | Cross-over; presentation of food           | Ghrelin: increase in both conditions |         |
| 50 Teff and Engelman, 1999b | 15 (M)            | Insulin, c-peptide, norepinephrine, epinephrine | Sham feeding                               | Insulin increase in modified sham feeding and food consumption conditions compared to fasting |         |
| 51 Teff et al., 1995b | 16 (M)             | Insulin                          | Sham feeding                               | insulin increase in baseline |         |
| 52 Teff et al., 1995c | 16 (M)             | Insulin                          | Sham feeding                               | Insulin increase in apple pie condition compared to other conditions |         |
| 53 Teff et al., 1995d | 15 (M)             | Insulin                          | Sham feeding                               | Insulin increase in apple pie condition compared to other conditions |         |
| 54 Teff and Engelman, 1996a | 8 (M)             | Insulin, c-peptide, glucagon     | Sham feeding                               | Insulin increase in both conditions from baseline |         |
| 55 Teff and Engelman, 1996b | 8 (M)             | Insulin, c-peptide, glucagon     | Sham feeding                               | Insulin increase in both conditions from baseline |         |
| 56 Teff et al., 1997b | 13 (F)             | Insulin                          | Sham feeding                               | Insulin increase in both conditions from baseline |         |
| 57 Teff et al., 1997c | 15 (M)             | Insulin                          | Sham feeding                               | Insulin increase in both conditions from baseline |         |
| 58 Teff et al., 1997d | 16 (M)             | Insulin                          | Sham feeding                               | Insulin increase in both conditions from baseline |         |
| 59 Teff et al., 1997e | 15 (M)             | Insulin                          | Sham feeding                               | Insulin increase in both conditions from baseline |         |
| 60 Teff et al., 1997f | 10 (M)             | Insulin                          | Sham feeding                               | Insulin increase in both conditions from baseline |         |
| 61 Teff et al., 1997g | 8 (M)              | Insulin                          | Sham feeding                               | Insulin increase in both conditions from baseline |         |

(continued on next page)
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

| First author and year | Sample size (sex*) | Hormones (Conditioned Response) | Triggering stimulus (Conditioned Stimulus) | Experimental design | Results |
|-----------------------|--------------------|----------------------------------|---------------------------------------------|---------------------|---------|
| 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. |
| Wijdemann 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. |
| Yamazaki and Sakaguchi, 1986 | 57 (M) | Insulin | Sweet taste of glucose on the tongue | Sham feeding | Insulin: increase in d-glucose condition compared to other conditions |
| Zhu et al., 2014 | 10 (M) | Insulin, ghrelin | Sham feeding | Cross-over; 4 conditions: water, high-fat, high-carbohydrate, high-protein food | 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.
| 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 |
| 2 Berthoud et al., 1980a | 7 rats | Insulin | Taste of saccharine | Cross-over; 6 conditions with prior ventromedial hypothalamic lesion of either: 2 × 1 ~ 1 saliné, 2 × 15 pg neutralized pancrea HCI, 2 × 50 pg neutralized pancrea HCI | Insulin: increase in saline condition compared to other conditions; decrease in 2 × 15 pg neutralized pancrea HCI condition and 2 × 50 pg neutralized pancrea HCI condition compared to other conditions |
| 3 Berthoud et al., 1981 | 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 |
| 4 Berthoud et al., 1980b | 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 sham feeding and feeding conditions compared to fasting Glucagon: increase in sham feeding and feeding conditions compared to fasting |
| 5 Dailey et al., 2012 | 7 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 Phenolamine enhanced this response |
| 6 Berthoud and Powley, 1990 | 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 sham feeding and feeding conditions compared to fasting Glucagon: increase in sham feeding and feeding conditions compared to fasting Phenolamine enhanced this response |
| 7 Coover et al., 1984 | 5 dogs | 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 Corticosterone: day 7 ~ increase in delayed fed group from baseline; day 20 ~ decreased in immediately fed from baseline |
| 8 Diamond and Bailey, 1983 | 5 dogs | Insulin | Food consumption | Cross-over; 3 conditions: saline injection, atropine sulfate injection, denervation of pancreas | Insulin: increase in saline condition compared to other conditions |
| 9 Dailey et al., 2012 | 7 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 Glucagon: increase in chow meal fed and high-fat meal fed groups compared to other conditions |
| 10 De Souza et al., 2001 | 22 (9 M, 13 F) dogs | Insulin | Taste of saccharine | 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 |
| 11 Diamond and Bailey, 1983 | 5 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 |
| 12 Drazen et al., 2006 | 26 wethers | Insulin | Time of feeding | Between-subjects; 2 conditions: 1 M glucose, 1 M glucose + 5 mM acarbose | Insulin: increase in both conditions from baseline |
| 13 Flatt and Bailey, 1983 | 22 (9 M, 13 F) dogs | Insulin | Time of feeding | Between-subjects; 2 conditions: 1 M glucose, 1 M glucose + 5 mM acarbose | Insulin: increase in both conditions from baseline |
| 14 Fischer et al., 1972 | 22 (9 M, 13 F) dogs | Insulin | Time of feeding | Between-subjects; 2 conditions: 1 M glucose, 1 M glucose + 5 mM acarbose | Insulin: increase in both conditions from baseline |
| 15 Gleninning et al., 2017 | 22 (9 M, 13 F) dogs | Insulin | Time of feeding | Between-subjects; 2 conditions: 1 M glucose, 1 M glucose + 5 mM acarbose | Insulin: increase in both conditions from baseline |
| 16 Gleninning et al., 2018 | 22 (9 M, 13 F) dogs | Insulin | Time of feeding | 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 | Insulin | Time of feeding | Between-subjects; 2 conditions: 1 M glucose, 1 M glucose + 5 mM acarbose | Insulin: increase in both conditions from baseline |

(continued on next page)
Table 2 (continued)

| Authors and year of the paper | N of subjects, specie, sex* | Hormone | Triggering stimulus | Design | Results |
|------------------------------|-----------------------------|---------|---------------------|--------|---------|
| Experiment 2                 | 10 lactating ewes (F)       | Insulin | Lactation cues      | Between-subjects; 2 conditions: vagotomy; hepatic, abomasal, pyloric and duodenal vagotomy; sham-operation | Insulin: increase in sham operation condition compared to other conditions |
|                            |                             |         |                     |        |         |
| 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 |
|                            |                             |         |                     |        |         |
| Karmann et al., 1992         | 7 geese                     | Insulin | Food consumption    | Within-subjects | Increase in insulin at the start of feeding |
|                            |                             |         |                     |        |         |
| 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 controlridge polypeptide: increase in teasing and sham feeding compared to control |
|                            |                             |         |                     |        |         |
| Kovacs et al., 1997          | 4 dogs                      | Gastrin | Sham feeding        | Between-subjects; 3 conditions: gastrin mononclonal antibody, keyhole limpet hemocyanin mononclonal antibody (control), atropine | Gastrin increased in all conditions compared to baseline |
|                            |                             |         |                     |        |         |
| 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. |
|                            |                             |         |                     |        |         |
| 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 |
|                            |                             |         |                     |        |         |
| Lushchak et al., 2015        | Drosophila flies (F)        | Insulin like peptides | Smell of cider vinegar | Between-subjects; 2 conditions: cinder vinegar smell, distilled water | Upregulation of genes encoding the glucagon-like hormone adipokinetic hormone, and insulin-like peptides in cinder vinegar condition compared to water condition |
|                            |                             |         |                     |        |         |
| 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 Corticosterone: restricted feeding standard chow: increase in anticipation compared to other conditions Corticosterone: restricted feeding high fat: increase post anticipation compared to other conditions |
|                            |                             |         |                     |        |         |
| 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 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 |
|                            |                             |         |                     |        |         |
| Nijjima 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 |
|                            |                             |         |                     |        |         |
| 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 |
|                            |                             |         |                     |        |         |
| Paparryphon 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 |
|                            |                             |         |                     |        |         |
| Storljen, 1985 Experiment 1  | 12 rats                     | Insulin | Complex stimulus (tone, light, smell) preceding feeding | Between-subjects; 2 conditions: intact, ventromedial hypothalamic 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 |
|                            |                             |         |                     |        |         |
| Strubbe and Steffens, 1975   | Rats (M)                    | Insulin | Food consumption    | Within-subjects | Insulin: early increase from baseline at the beginning of feeding |
| Strubbe, 1992                |                             |         |                     |        |         |
| Tonoaki 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 |
|                            |                             |         |                     |        |         |
| Vahl et al., 2010            | Rats (M)                    | Glucagon-like peptide-1, insulin | Time of feeding | Between-subjects; 2 conditions: stimulant diet, basal diet | GluP-1: increase in meal fed condition compared to control |

(continued on next page)
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), obestin (n = 1), peptide YY (n = 1), anandamide (n = 1), 2-arachidonoyl-glycerol (n = 1), palmitoylethanolamide (n = 1), oleoylthanolamide (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
Overview of the direction of the results.

Table 3

| 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                | 8/8                                              | 4/5                                              |
|                          | Sham feeding        | –                                                | –                                                |
|                          | Expectation of food | –                                                | –                                                |
|                          | 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          | 0/1                                              | –                                                |
| Pancreatic polypeptide   | Sweet taste         | –                                                | 0/3                                              |
|                          | Sham feeding        | 1/1                                              | 7/8                                              |
|                          | Food                | –                                                | 1/2                                              |
|                          | Presentaiton        | –                                                | –                                                |
| Ghrelin                  | Sweet taste         | –                                                | 0/1                                              |
|                          | Food                | –                                                | 1/1                                              |
|                          | Consumption         | –                                                | –                                                |
|                          | Sham feeding        | –                                                | 4/4                                              |
|                          | Expectation of food | –                                                | 2/3                                              |
|                          | Time                | 3/3                                              | 2/2                                              |
|                          | Food                | –                                                | 0/1                                              |
|                          | Presentation        | –                                                | 1/1                                              |
|                          | Sham feeding and food consumption | – | 1/1 |
| Glucagon                 | Sweet taste         | 1/1                                              | 0/1                                              |
|                          | Food                | –                                                | 1/1                                              |
|                          | Consumption         | –                                                | 1/2                                              |
|                          | Sham feeding        | –                                                | –                                                |
|                          | Expectation of food | –                                                | –                                                |
|                          | Time                | 0/1                                              | –                                                |
|                          | Sound               | –                                                | 0/1                                              |
|                          | Food                | –                                                | –                                                |
|                          | Presentation        | –                                                | –                                                |
|                          | Expectation of food and sweet taste | – | – |
|                          | Oral rinsing with glucose | – | – |
|                          | Complex stimulus    | Pictures of food | – | 0/1 |
|                          | Sham feeding and food consumption | – | 1/1 |
|                          | Discussion          | about food                                       | –                                                |
|                          | C-peptide           | Food consumption | – | 1/1 |
|                          | Shen feeding        | –                                                | 2/3                                              |
|                          | Pictures of food    | –                                                | 0/1                                              |
|                          | Expectation of food | –                                                | 0/1                                              |
|                          | Time                | 2/2                                              | –                                                |
|                          | Food consumption   | –                                                | 0/1                                              |

Table 3 (continued)

| Hormone                  | Triggering stimulus | Proportion of positive results in animal studies | Proportion of positive results in human studies |
|--------------------------|---------------------|-------------------------------------------------|------------------------------------------------|
| Gastrin                  | Sham feeding        | –                                                | 2/2                                              |
|                          | Discussion          | –                                                | 1/1                                              |
| Leptin                   | Expectation of food | –                                                | 0/1                                              |
|                          | Time                | –                                                | 0/1                                              |
|                          | Food                | –                                                | 0/1                                              |
|                          | Presentation        | –                                                | –                                                |
| Cortisol/corticosterone  | Expectation of food | –                                                | 1/1                                              |
|                          | Time                | 4/4                                              | –                                                |
|                          | Sound               | –                                                | 1/1                                              |
| Norepinephrine           | Sham feeding        | –                                                | 0/1                                              |
|                          | Food                | –                                                | 0/1                                              |
|                          | Presentation        | –                                                | –                                                |
| Gastric inhibitory       | Sound               | –                                                | 0/1                                              |
| polypeptide              | Obestatin           | Sham feeding                                     | –                                                |
|                          | Peptide YY          | Expectation of food                              | –                                                |
|                          | Anandamide          | Expectation of food                              | –                                                |
|                          | 2-arachidonoylglycerol | Expectation of food                      | –                                                |
|                          | Oleoylethanolamide  | Expectation of food                              | –                                                |
|                          | Palmitoylethanolamide | Expectation of food                        | –                                                |
|                          | Secretin            | Sham feeding                                     | –                                                |
|                          | Cholecystokinin     | Sham feeding                                     | 0/1                                              |
|                          | Adrenocorticotropic hormone | Expectation of food                        | 0/1                                              |
|                          | Motilin             | Time                                             | 0/1                                              |
|                          | Inulin-like peptides | Smell                                           | 1/1                                              |
|                          | Growth hormone      | Time                                             | 1/1                                              |

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 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 = 1), discussion about food (n = 1), presentation of food pictures (n = 1), 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, palmitoylthetanolamide 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; Sjostrom 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 (Buyschaert et al., 1985; Glasbrenner et al., 1995). Absence of cephalic secretin release was found in patients with pancreatic insufficiency (Wojdemann 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 (Feillett, 2010).

It is still not entirely known to what extent 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., 1986; 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 naturally 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 where 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 (Feillett, 2010; MislBerger, 1994) but might be of a smaller magnitude than in cases where 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 non-nutritive or low caloric substance alone (Abdallah et al., 1997; Bruce et al., 1987; Cedernaes et al., 2016; HärteI 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 (Buyschaert et al., 1985; Glasbrenner et al., 1995; Goldschmidt et al., 1990; Teff et al., 1995, Teff et al., 1993a,b, 1991). Moreover, a number of studies found that there are some differences in the taste-stimulated food anticipatory responses (Belli et al., 1985; Dhillion 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...
Cognition might also explain the discrepancy in the results between the consumed a high caloric shake in comparison to the participants who was larger in magnitude in participants who thought that they had demonstrated that the decrease of ghrelin levels after food consumption et al., 2015). Moreover, Crum and colleagues (Crum et al., 2011) linked to satiety (Kurrasch et al., 2007). Animals with lesions of this area acetylcholine receptors, was shown to abolish cephalic insulin (Sjöström et al., 1980) and pancreatic polypeptide release (Veeldal 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) lead 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 (Buyschaert et al., 1985; Glasbrener et al., 1995), obesity (Brede et al., 2017; Johnson and Wildman, 1983; Osuma et al., 1986; Sjöström et al., 1980), eating disorders (Broberg and Bernstein, 1989; Monteleone et al., 2010, 2008; Moyer et al., 1993), pancreatic insufficiency (Wojdemann et al., 2008; Wiesner kienzle et al., 2001), chronic pancreatitis (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., 2013; 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 "Estrogen"[Mesh] OR "Gonadotropin-Releasing Hormone"[Mesh] OR "Follicle Stimulating Hormone"[Mesh] OR "Oxytocin"[Mesh] OR "Prolactin"[Mesh] OR "Dehydroepiandrosterone"[Mesh] OR "Progestogen"[Mesh] OR "Thyrotropin"[Mesh] OR "Thyroxine"[Mesh] OR "Glucagon"[Mesh] OR "Glucagon-Like Peptide"[Mesh] OR "Ghrelin"[Mesh] OR "C-Pep tile"[Mesh] OR "Insulin"[Mesh] OR "Pancreatic Polypeptide"[Mesh] OR "Leptin"[Mesh] OR "Incretins"[Mesh] OR "Renin"[Mesh] OR "Angiotensin"[Mesh] OR "Aldosterone"[Mesh] OR "Vasopressin"[Mesh] OR "Epinephrine"[Mesh] OR "Norepinephrine"[Mesh] OR "Melatonin"[Mesh] OR "Cholecystokinin"[Mesh] OR "Human Growth Hormone"[Mesh] OR "Insulin-Like Growth Factor 1"[Mesh] OR "Melanocyte-Stimulating Hormones"[Mesh] OR "Blood Glucose"[Mesh] OR "Glucose"[Mesh] OR "Glucocorticoids"[Mesh] OR "Endocrine"[Mesh] OR "Thyroid Hormones" OR "Adrenocortical Hormone" OR "Adrenocorticotropic Hormone" OR "Corticotropin-Releasing Hormone" OR "Endocrine System" OR "Neuroendocrine" OR "Endocrine System" OR "Thyroid Hormones" OR "Adrenocorticotropic Hormone" OR "Adrenocorticotropic Hormone" OR "Corticotropin-Releasing Hormone" OR "Endocrine System" OR "Neuroendocrine" OR "Endocrine System" OR "Thyroid Hormones" OR "Adrenocorticotropic Hormone" OR "Adrenocorticotropic Hormone" OR "Corticotropin-Releasing Hormone" OR "Endocrine System" OR "Neuroendocrine" OR "Endocrine System" OR "Thyroid Hormones" OR "Adrenocorticotropic Hormone" OR "Adrenocorticotropic Hormone" OR "Corticotropin-Releasing Hormone" OR "Endocrine System" OR "Neuroendocrine" OR "Endocrine System" OR "Thyroid Hormones" OR "Adrenocorticotropic Hormone" OR "Adrenocorticotropic Hormone" OR "Corticotropin-Releasing Hormone" OR "Endocrine System" OR "Neuroendocrine" OR "Endocrine System" OR "Thyroid Hormones" |

AEA (HSR-2014-03-003-09-11, granted to A. Skvortsova et al.)

(continued on next page)
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.
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