



How neural mediation of anticipatory and compensatory insulin release helps us tolerate food[☆]

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ABSTRACT

Learned anticipatory and compensatory responses allow the animal and human to maintain metabolic homeostasis during periods of nutritional challenges, either acutely within each meal or chronically during periods of overnutrition. This paper discusses the role of neurally-mediated anticipatory responses in humans and their role in glucoregulation, focusing on cephalic phase insulin and pancreatic polypeptide release as well as compensatory insulin release during the etiology of insulin resistance. The necessary stimuli required to elicit CPIR and vagal activation are discussed and the role of CPIR and vagal efferent activation in intra-meal metabolic homeostasis and during chronic nutritional challenges are reviewed.

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1. Introduction

In the paper entitled “The Eating Paradox: How We Tolerate Food” [1], the author Stephen C. Woods proposes the analogy between food ingestion and drug consumption and argues that physiological and behavioral tolerance to the daily consumption of nutrients must develop to limit metabolic disruptions and maintain homeostasis. Learned anticipatory responses are hypothesized to “minimize the impact of meals” and cephalic phase insulin release (CPIR) is used as an example of a conditioned physiological response which adapts to changing levels of food intake and contributes to glucoregulation. In the present article, I will review what is known about anticipatory responses and discuss the hypothesis of their contribution to metabolic homeostasis, focusing primarily on hormonal responses in humans. Furthermore, I will extend the hypothesis by postulating how impairments in vagally-mediated adaptive responses may be involved in the etiology of insulin resistance.

1.1. Anticipatory responses: historical overview

Anticipatory responses were first identified by a series of elegant experiments conducted by Ivan Pavlov at the turn of the century [2]. Pavlov demonstrated that the secretion of a variety of physiological responses including saliva, gastric acid and pancreatic enzymes could all

be entrained by repeated pairing of external signals such as a bell or the sight of a meal, to meal ingestion. He further demonstrated that the mere taste of food in the oral cavity, independent of nutrient digestion and absorption, could elicit these same responses. To ensure that no nutrients were being absorbed, the dogs were implanted with esophageal and gastric fistulae preventing the nutrients in the oral cavity from reaching the stomach and intestine. In another set of experiments, gastric and pancreatic enzyme secretions were inhibited by severing the vagus nerve, thereby demonstrating mediation by the parasympathetic branch of the autonomic nervous system [2]. The involvement of the brain in the mediation of these responses resulted in the coinage of the term “cephalic phase responses” referring to coming from the head. Pavlov’s studies provided the key criteria of the current definition of an anticipatory or cephalic phase response; neurally-mediated, anticipatory responses occurring prior to nutrient absorption.

Identification of anticipatory hormonal release only came many decades later with the development of the radioimmunoassay which facilitated measurement of hormones, such as insulin and glucagon. Early experiments examined the role of learning in controlling blood glucose levels. Insulin was administered in a Pavlovian conditioning paradigm to cause conditioned changes in blood glucose levels. In these experiments, humans, dogs or rats were injected with insulin, inducing hypoglycemia and subsequent physiological perturbations [3–8]. After repeated administration of insulin, saline was then injected. Blood glucose levels typically dropped and increases in plasma insulin were hypothesized to mediate the decline in blood glucose levels. Some studies utilizing more physiological (i.e. lower) doses of insulin reported increases in plasma glucose. Thus, the directionality of the conditioned responses was controversial [9]. Neural mediation of the conditioned hypoglycemia was confirmed by

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vagotomy as well as administration of the muscarinic antagonist, atropine which inhibits the binding of acetylcholine to receptors on the pancreas [10]. The importance of dose and the temporal relationship between the unconditioned stimuli and response and a general review of these studies is provided in the paper by Woods and Kulkosky [8]. Over the next couple of decades, research in this area moved away from these non-physiological paradigms and migrated towards studies that addressed the relationship of the conditioned insulin response to food intake and how the conditioned insulin response contributed to glucose homeostasis [8, 11–15].

2. Anticipatory or cephalic phase insulin release (CPIR): definition and identification

Currently, anticipatory or cephalic phase insulin release (CPIR) is defined as insulin release which occurs prior to nutrient absorption in response to sensory stimulation of the oral cavity by the taste of food or food ingestion. In humans, the response is typically characterized by a rise in plasma insulin levels that occurs independently of increases in blood glucose, peaking within 4 min after sensory stimulation and returning to baseline by 8–10 min post stimulation (Fig. 1, left and middle graph). As the response occurs rapidly, is of small magnitude (approximately 1% of normal post prandial insulin release) and exhibits a large variability, identification of CPIR requires careful and rapid blood sampling, adequate baseline sampling and an appropriate control condition [16, 17]. Furthermore, for nutrients which are rapidly absorbed such as liquids, distinguishing between neural and nutrient-mediated insulin release can be problematic. To differentiate between neural and nutrient stimulation, animals can be implanted with oral or gastric fistulas to uncouple the effects of oral stimulation from absorption, creating a sham-feeding condition [15, 18]. In humans, subjects are often requested to perform a modified sham-feed in which food is tasted, chewed and then expectorated [17]. Neural mediation of hormonal release has been verified by studies showing inhibition of the response by the muscarinic antagonist atropine [18] as well as vagotomy in animals [13, 19–21]. Supporting evidence for the neural mediation of CPIR, is provided by the lack of CPIR in rats [22] and humans who have undergone pancreas–kidney transplantation and have no neural innervation of the transplanted pancreas [23].

3. Cephalic phase insulin and pancreatic polypeptide release: window into vagal activation

At the onset of food ingestion, activated vagal efferent fibers terminating on the pancreas release acetylcholine which binds to

muscarinic receptors on the pancreatic islet. Muscarinic receptor activation stimulates the release of insulin as well as other hormones stored in the pancreatic islet [24–26]. Glucagon localized in the α -cell and pancreatic polypeptide (PP) found in the delta cells are both released in response to acetylcholine. Insulin and glucagon are under complex regulatory control responding to activation or inhibition by multiple nutritional and neural signals including circulating plasma glucose levels, amino acids and neurotransmitters from both branches of the autonomic nervous system. In contrast, PP is released only in response to vagal activation (i.e. not to increases in glucose levels) and is not inhibited by the sympathetic nervous system [26]. As PP release is dependent on vagal efferent activation, the hormone can be used as a marker of vagal activity. This provides an important biological tool for the measurement of vagal activation since acetylcholine released by the vagus nerve cannot be directly measured in plasma due to its rapid degradation in the synaptic cleft, rendering all measurements of vagal efferent activity in humans indirect. Furthermore, as the magnitude of PP release to sham-feeding is much larger than CPIR (Fig. 1, right graph), this allows for the measurement of graded responses to stimuli that is not possible with CPIR.

While increases in cephalic phase insulin release would be expected to occur coincident with cephalic phase pancreatic polypeptide (CPPP) since both are dependent on vagal activation, we [27] and others [28] have reported increases in CPPP independent of CPIR. This can occur on an individual level as illustrated in Fig. 2 where one individual (upper graphs) exhibits robust insulin and PP responses to a sham-feed while the individual in the lower graphs, does not exhibit a CPIR and the PP response is modest. Alternatively, we have also seen group responses where PP is increased to a sham-feed but CPIR does not occur. The lack of an increase in anticipatory insulin release in the presence of vagal activation may be due to a simultaneous activation of the sympathetic nervous system resulting in adrenergic inhibition of insulin release [1, 29]. Coincident activation of both branches of the autonomic nervous system is observed during both hyper- and hypo-glycemia [30, 31] and in fact, cephalic phase noradrenaline release has been reported in animals [29, 32, 33]. Alternatively, if the mean group response to a stimulus shows an increase in both cephalic phase insulin and PP but on an individual level, some subjects do not exhibit a CPIR in the presence of a PP response, it could be interpreted that this individual did experience vagal activation to the particular stimulus but that a stress response inhibited insulin release. In contrast, an absence of both cephalic phase PP and CPIR provides convincing evidence that vagal efferent activation at the pancreas did not take place at all. Thus, in humans, monitoring both hormones can provide insight into how experimental stimuli and paradigms influence anticipatory responses. Unfortunately, the PP assay for rat and mouse pancreatic polypeptide is

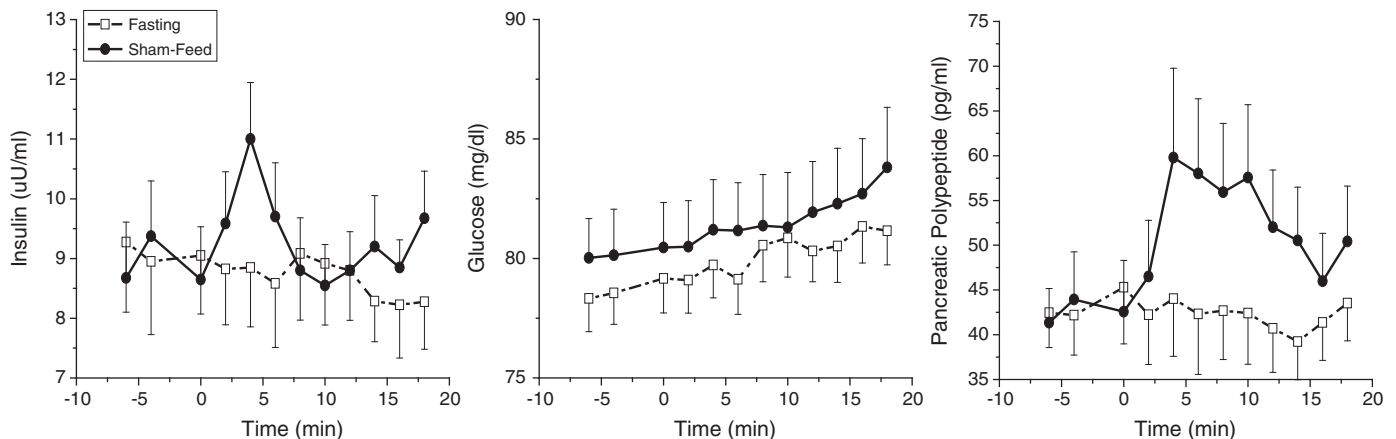


Fig. 1. Cephalic phase insulin release (left graph), plasma glucose levels (middle graph) and cephalic phase pancreatic polypeptide release (right graph) during a sham-feed (solid circles) compared to fasting (open squares) in normal weight humans (mean $\pm$ s.e., $n = 10$).

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