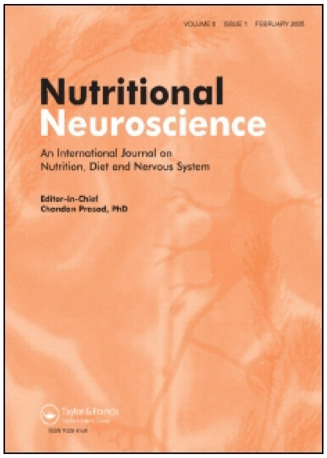

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Effects of intragastric administration of predigested nutrients on food intake, body weight and taste acceptability: Potential relevance of the cephalic/neural phase of digestion

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Effects of intragastric administration of predigested nutrients on food intake, body weight and taste acceptability: Potential relevance of the cephalic/neural phase of digestion

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Abstract

In this study we analyzed the effect of the intragastric administration of partially digested and natural nutrients on subsequent food intake, body weight and flavor acceptability in rats. The results showed that enterally administered natural nutrients reduced the subsequent ingestion of food to a greater degree compared with the same nutrients in partially digested form. This greater reduction does not appear to be due to a higher nutritional effect of the former, because the body weight of both groups of animals was similar. Animals intragastrically administered with partially digested nutrients developed an acceptance response to a previously paired flavored stimulus, in contrast to animals receiving natural nutrients under the same conditions. These results are interpreted in terms of the cephalic phase of digestion and may be relevant to the treatment of clinical symptoms associated with enteral feeding.

Keywords: *Cephalic phase, enteral nutrition, food intake, taste avoidance, taste preference*

Introduction

The function of the gastrointestinal system in food intake has been widely researched by direct administration of nutrients to different parts of this system and analysis of the subsequent food intake. Thus, the effects on intake of administering different macronutrients to the stomach (Berkun et al. 1952; Phillips and Powley 1996; Cox et al. 2004a,b), liver (Tordoff and Friedman 1986), and various segments of the small intestine (Canbely and Koopmans 1984; Chapman et al. 1999; Cox et al. 2004a,b) have been investigated. In general, these authors reported that nutrients directly administered into the gastrointestinal tract significantly reduce subsequent food intake. This finding has been interpreted in terms of satiation, concluding that the direct administration of foods to the digestive tract produces a rapid and significant reduction in nutritional deficit.

Several clinical and experimental studies have suggested that the intragastric (i.g.) administration of predigested nutrients can facilitate the digestive process. Thus, in the renowned "Tom case" (Wolf and Wolf 1947; Powley 1977; Zafra et al. 2006), the patient's digestion was not optimal when food was directly injected into the stomach and he was poorly nourished. However, when Tom's request to taste and chew food before its i.g. administration was granted, he gained weight and had a good appetite (Wolf and Wolf 1947). Likewise, when animals had to choose between two different gustatory solutions, one associated with the i.g. administration of partially digested foods (foods ingested orally by donor animals and pumped from their stomachs after remaining there for a period of time)

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and the other with i.g. physiological saline, they chose the solution linked to the predigested nutrients and strongly rejected the gustatory stimulus associated with saline administration (Puerto et al. 1976a,b; Zafra et al. 2002, 2006). However, these positive effects of the i.g. administration of nutrients are not observed in animals when natural, non-predigested foods are used (Deutsch et al. 1976; Puerto et al. 1976b; Zafra 2000, 2005).

Experiment 1 of the present study was designed to examine the effects of enteral administration of partially digested nutrients on the subsequent intake of the animals, comparing it with the effects of enteral administration of the same foods in a natural, non-partially digested condition. As originally shown by Pavlov (1910) and later by many others (Molina et al. 1977; Brand et al. 1982), partially digested nutrients contain a certain amount of digestive secretions and their nutritional value may, therefore, differ from that of natural foods. For this reason, the possible effects on body weight of each food were compared with the effect produced by physiological saline administration. In addition, a second experiment was designed to examine the effects of enteral administration of the partially digested and natural foods in a flavour acceptability task.

Materials and methods

Subjects

Male Wistar rats (250–330 g each at the beginning of the experiment) from the breeding colony at the University of Granada were used. Subjects were individually housed in methacrylate cages (30 × 15 × 30 cm), which also served as training chambers during the experiment. The lateral sides of the cages were black and opaque; the front and back sides were transparent. The front side had two 1.6-cm holes at the same distance from the centre and edges and at the same height above the floor of the cage. By means of these orifices, the animal had access to spouts through which the water was administered. The room temperature was maintained on a 12-h light/12-h dark cycle at 21–23°C. All handling was done during the light phase. The animals were allowed a 2–3 day adaptation period, when they remained in their cages and had free access to a standard pelleted stock diet (Panlab, S.L. Barcelona) and water before surgery. All behavioral procedures and surgical techniques were conducted in accordance with the Animal Care and Use Guidelines established by Spanish Royal Law 223/1988. Every effort was made to use the minimum number of animals in these experiments.

Surgical procedure

Rats were anesthetized with sodium pentothal (46.3 mg/Kg, ip; sodium thiopental, Abbot Laboratories) and an intragastric catheter was implanted using a modified version of the procedure developed by Deutsch and Koopmans (1973). In brief, a silastic tube (Silastic-Medical Grade Tubing, Dow Corning Corp., Michigan, USA) was implanted into the cardiac portion of the stomach, routed through the abdominal muscle wall, and placed under the skin at the back of the neck. Stitching was performed as needed to help close the wounds, and the rats received an intramuscular 0.1 ml dose of penicillin (1000000 IU, Penilevel Lab. Ern, Barcelona, Spain) as a prophylaxis against infection. The same procedure was used for the donor rats except that they were implanted with two catheters, one on each side of the animal.

Experiment 1

Twenty-five naïve animals were used in this study. They were randomly assigned to one of three groups: six were included in a "partially digested diet" group, six in a "natural diet" group, and five in a control group ("physiological saline"). Eight donor rats were additionally used to provide partially digested nutrients. A period of 7 days was allowed for postoperative recovery, with free access to food and water. After the recovery and before the start of the experiment, there was a three-day pre-training period: on each day, the rats were injected via the catheter with 0.5 ml of water at room temperature; they were then offered 12 g (on first 2 days) or 7 g (on the third day, in order to minimize gastric contents on the next day) of standard pelleted stock diet (Pienso Compuesto Sanders, Unidad Alimentaria Sanders, Granada). Donor rats were placed in a different room and trained for 7 days to ingest a liquid diet (Ideal Evaporated whole milk, 50% diluted, Nestlé, Barcelona); 100 ml of this liquid diet contained 5.75 g of carbohydrates, 3.93 g of fat and 3.93 g of protein (total energy: 74.37 Kcal). The diet was offered for several hours both in the morning and afternoon. Water was offered for 10 min during the evening of each day, although the animals generally did not consume it. During the last 4–5 days of this pre-training period, the ingested milk was daily pumped out from the stomach to habituate the animals to the extractions. After this, they were returned to the liquid diet to keep them nourished during the experimental period.

The experiment began after the three-day pre-training period. The experiment started with withdrawal of the water available until that time. One hour later, each subject received one of three treatments according to their assigned group: the "partially digested diet" group received i.g. 8 ml of partially digested liquid diet (Ideal Evaporated whole milk, 50% diluted, Nestlé, Barcelona) that had been pumped out of the stomach of the donor rats (the food remained in stomach of donor rats for at least 30 min before being pumped out); the "natural diet" group received i.g. 8 ml of liquid diet (Ideal Evaporated whole milk, 50% diluted. Nestlé. Barcelona); and the "physiological saline" control group received i.g. 8 ml of isotonic physiological saline (Apiroserum. Lab. YBIS, Madrid). These substances (liquid diet or physiological saline) were administered at a rate of 1.6 cc/min through two polyethylene connectors of sufficient length to allow the animals freedom of movement.

When this treatment was concluded, 7 g of standard rat pelleted stock diet were offered (Sanders, Unidad Alimentaria Sanders, Granada). In the first part of the experiment, the first three days, the time interval between the i.g. administration of the substance and the presentation of solid food was 60 min; on the three following days, the interval was 90 min, and on the last three days, it was 30 min. Assignment of these time periods was established at random. The total amount of post-infusion food consumed was measured at 30 and 60 min after presentation of the solid food. After this experimental session, the animals again had free access to water until the next session on the following day. Body weight was measured daily through the experiment.

Experiment 2

Experiment 2 was designed to test whether the enteral administration of the natural and partially digested nutrients used in experiment 1 is experienced by the subjects as a rewarding event. The positive nature of the enteral administration of nutrients can be determined by means of taste discrimination tests. The usual procedure is to offer a gustatory stimulus followed by the administration of rewarding substances (Garcia et al. 1967; Puerto et al. 1976b; Tordoff 2002; Zafra et al. 2002). With this background, animals in this experiment underwent a learning test that consisted of presentation of a gustatory stimulus immediately followed by intragastric administration of the natural or partially digested foods. The degree of acceptance shown by animals for the associated taste was then analyzed.

Subjects were 20 male Wistar rats that were randomly assigned to one of three groups: "partially digested diet" group ($n = 5$), "natural diet" group ($n = 5$), and donor group ($n = 10$). After surgery, all animals were allowed a recovery period of 7–10 days, with food and water available *ad libitum*. They then underwent a 7-day adaptation period during which they were trained to receive solid food and water only twice a day: once in the morning and once in the afternoon, they were allowed access to water for 15 min, after which they were offered 7.5 g of pelleted stock diet (Pienso Compuesto Sanders, Unidad Alimentaria Sanders, Granada). The training of donor rats was identical to that described in experiment 1.

After seven pre-training days, the experimental learning test began. On the first morning, animals in the "natural diet" and "partially digested diet" groups were offered a burette containing water flavored with vanilla (McCormick Co. Inc., San Francisco, CA, at a concentration of 0.5 cc/100 ml of water) for 7 min. The burette was then withdrawn and the amount consumed by each animal was recorded. Each animal immediately received one of two treatments according to their assigned group: the "partially digested diet" group received i.g. 12 ml of a partially digested liquid diet pumped from stomach of donor rats and the "natural diet" group received i.g 12 ml of liquid diet (Ideal Evaporated whole milk, 50% diluted; Nestlé, Barcelona). The entire treatment was repeated in the afternoon, starting the experimental sessions at 17:00. After the treatment sessions, the animals had access to water for 10 min.

The increase or reduction in intake of the flavor (vanilla) associated with intragastric administration of the two types of food (natural vs. pre-digested) was used as an index of the acceptability of these nutrients.

Statistical analyses

Data are expressed as means ± SEMs. All statistical analyses were performed by using Statistica, version 5.1 (from Statsoft, Tulsa, USA), with $P < 0.05$ considered statistically significant. The significance of mean differences among groups in food intake (for each interval and measurement), body weight, and taste consumption was determined by means of analysis of variance. In accordance with our study hypothesis, planned comparisons were performed when appropriate.

Results

Experiment 1

During experiment 1, the catheter became detached from one animal of the "partially digested diet" group. For this reason, the data from only five subjects were analyzed in the 90 min interval; and for the same reason, the ANOVA of the third part (30 min time interval) only included four subjects from the partially digested diet group. The catheter also became detached in two animals of the control group. However, in this case, data from all the animals were included in the statistical analysis, because previous experiments have demonstrated that administration and non-administration of physiological saline have the same effect on nutritional behavior (Kohn 1951). In the statistical analysis of the body weight data, only four animals from the "partially digested diet" group were included, i.e. those with data for all three parts of the experiment.

In all three parts of the experiment, inter-group differences were analyzed by using repeated-measures ANOVA (days, recording time). In all analyses (30-min interval, 60-min interval, or 90-min interval), the group, days, and measurement time (30 or 60 min) variables were all significant [30-min interval: group variable, $F(2,12) = 6.378$, $P < 0.0129$;

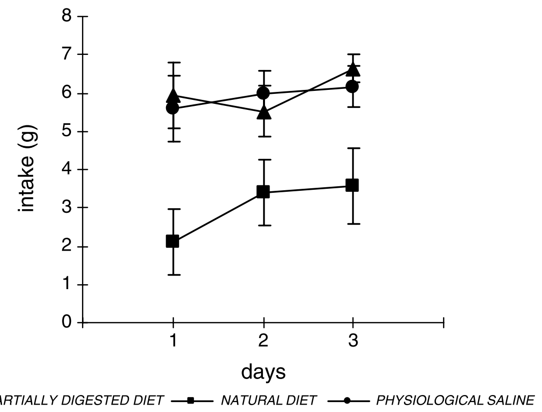

Figure 1. Mean amounts of standard pelleted stock diet consumed by the subjects of experiment 1 during the 60 min post-administration interval (measured 60 min after its presentation).

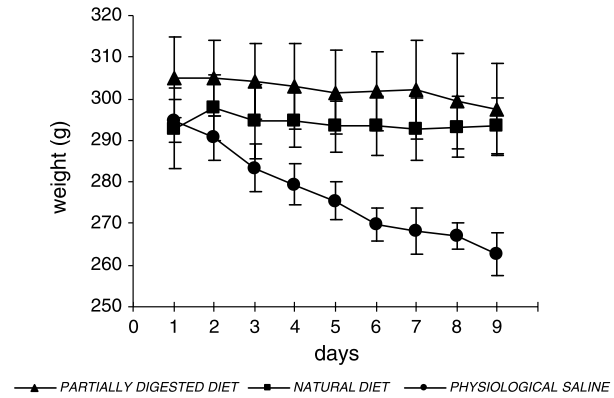

Figure 2. Variations in body weight of subjects in experiment 1.

days variable, F(2,24) = 3.609, $P < 0.0426$; and measurement time, F(1,12) = 15.469, $P < 0.0019$. 60-min interval: group variable, F(2,14) = 5.869, $P < 0.014$; days variable, F(2,28) = 6.302, $P < 0.0054$; and measurement time, F(1,14) = 16.870, $P < 0.001$. 90-min interval: group variable, F(2,13) = 5.504, $P < 0.018$; days variable, F(2,26) = 4.363, $P < 0.0232$; and measurement time, F(1,13) = 14.102, $P < 0.0024$)]. Figure 1 is representative of these data.

Planned inter-group comparisons all showed significant differences between "partially digested diet" and "natural diet" groups [30-min interval: F(1,12) = 8.47, $P < 0.013$; 60-min interval: F(1,14) = 8.74, $P < 0.01$; 90-min interval: F(1,13) = 9.26, $P < 0.009$] and between "natural diet" and "physiological saline" groups [30-min interval: F(1,12) = 9.69, $P < 0.008$; 60-min interval: F(1,14) = 8.58, $P < 0.01$; 90-min interval: F(1,13) = 6.54, $P < 0.023$]. However, no differences were observed between "partially digested diet" and "physiological saline" groups [30-min interval: F(1,12) = 0.00009, $P < 0.99$; 60-min interval: F(1,14) = 0.0121, $P < 0.913$; 90-min interval: F(1,13) = 0.215, $P < 0.649$].

The body weight group x days interaction was significant [F(16,96) = 13.91, $P < 0.001$], apparently due to the decrease in weight observed in the "physiological saline" group (Figure 2). Thus, planned intergroup comparisons showed no differences in body weight between "natural diet" and "partially digested diet" groups either on the first day [F(1,12) = 0.79, $P < 0.39$] or on the last day [F(1,12) = 0.15, $P < 0.7$] of the experiment. However, although no differences were observed between the "natural diet" and "physiological saline" groups or between the "partially digested diet" and "physiological saline" groups on the first day of the experiment [F(1,12) = 0.02, $P < 0.8$ and F(1,12) = 0.52, $P < 0.48$, respectively], significant differences between these groups were found on the last day [F(1,12) = 9.29, $P < 0.01$ and F(1,12) = 9.76, $P < 0.008$, respectively].

Experiment 2

The mean amounts (morning/afternoon) of the gustatory stimulus (vanilla) consumed by the subjects were analyzed by an ANOVA. This analysis showed that the two groups differed in the amount of gustatory stimulus consumed [F(1,8) = 8.488, $P < 0.019$; Figure 3], days [F(4,32) = 8.78, $P < 0.001$] and that the group x days interaction was significant [F(4,32) = 6.449, $P < 0.001$]. Planned inter-group comparisons between days showed that the differences were already significant on the second day [day 1: F(1,8) = 0.762, $P < 0.408$; day 2: F(1,8) = 5.653, $P < 0.045$; day 3: F(1,8) = 9.589, $P < 0.015$, day 4: F(1,8) = 8.026, $P < 0.022$, day 5: F(1,8) = 10.069, $P < 0.013$]. In other words, whereas there were no differences between the two groups on the first day, before they had gained experience of the

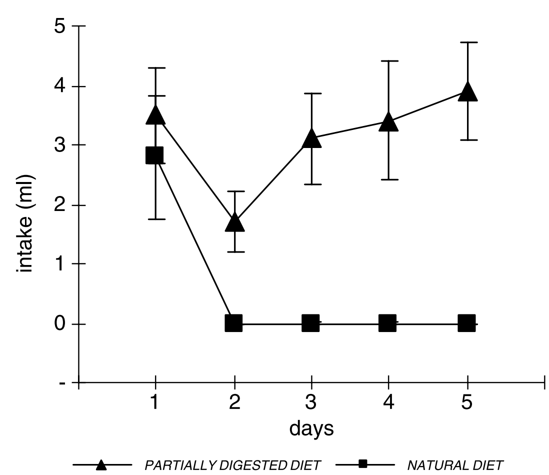

Figure 3. Mean amounts (morning/afternoon) of the gustatory stimulus (vanilla) consumed by the subjects in experiment 2.

administrations, by the end of the training, on day 5, there were marked differences.

The acceptability of the flavor associated with the i.g.-administered nutrients was examined by means of an intragroup analysis comparing the first- and last-day intake of the animals, showing no differences for the "partially digested diet" group [$F(1,8) = 1.54$, $P < 0.24$] but significant differences for the "natural diet" group [$F(1,8) = 14.614$, $P < 0.005$].

Discussion

It may be concluded from the data obtained in experiment 1 that the enteral administration of nutrients produces a reduction in subsequent intake, as observed by other authors (Berkun et al. 1952; Canbely and Koopmans 1984; Phillips and Powley 1996). This reduction was not observed when the same nutrients were administered in partially digested form, in which case the effect was comparable to that of isotonic physiological saline (Figure 1). In general, this effect was maintained regardless of the time interval between the enteral feeding episode and the start of the subsequent solid food intake. Likewise, the effect was maintained at both 30 and 60 min after presentation of the food.

At first sight, these results may appear to be a consequence of the scant nutritional value of the partially digested foods in comparison with their natural form. However, this interpretation is challenged by the body weight data. Interestingly, and as can be observed in Figure 2, there were no differences in body weight during the experiment between the animals administered with a natural diet and those administered with a partially digested diet. In contrast, the weight of both groups was significantly different from that of the animals receiving physiological saline, which had no caloric content. Therefore, the differences in subsequent intake between the animals receiving i.g. administration of natural or partially digested food are apparently not produced by differences in nutritional values or satiation effects between the nutrients.

Furthermore, as can be observed in Figure 3, the animals in the "partially digested diet" group developed an acceptance response for the previously presented flavor, indicating that they experienced the administration of these foods as a positive event. The differences between the two groups must be solely due to the specific treatment applied (normal vs. partially digested evaporated milk), since differences were not observed on day one of the experiment when the animals had no experience of the consequences of the nutrient administration (in this experiment, on the second day of the learning test, the "partially digested diet" group showed a major decrease in the consumption of the gustatory stimulus. This may be because the enteral administration of substances was a novel event for these animals. After experiencing the rewarding effect of the foods, the subjects showed a rapid adaptation, and eventually reached levels that were even higher than those observed on the first day, before any enteral administration).

The findings of our experiments are consistent with those obtained in taste preference tasks (Puerto et al. 1976a,b; Zafra et al. 2002). The preference for gustatory stimuli associated to the enteral administration of nutrients is dependent on the natural or partially digested nature of the foods.

At least under the conditions of our experiments, these contrasting effects of enterally administered natural and partially digested evaporated milk may be explained in terms of the well-known cephalic/neural phase of digestion (Pavlov 1910; Molina et al. 1977; Puerto 1977; Zafra et al. 2006). When nutrients are directly injected into the gastric cavity, all neuroendocrine responses triggered by this digestive process are eliminated. Natural foods arrive at the gastrointestinal system in a less physiological manner, slowing and altering the digestion, as originally demonstrated by Pavlov and subsequently by numerous other authors, underlining the nutritional importance of cephalic/-neural systems (Pavlov 1910; Zafra et al. 2006).

In addition, the consequences of obviating the cephalic phase are not only reflected in the subsequent digestion of the foods but also in other digestive processes, with an acceleration of gastric emptying, intolerance to glucose, reduction in lipolysis and increase in body weight (Molina et al. 1977; Rothwell and Stock 1978; Kaplan et al. 1993,1997; Yamashita et al. 1993; Friedman et al. 1996; Mattes 1996; Teff and Engelman 1996); it has even been reported that major damage to the intestinal mucosa can be produced (Friedman et al. 1996; Horn et al. 1996; Ramirez et al. 1997). This may in turn explain the reduction in subsequent intake observed in studies of enteral feeding.

Enteral feeding is believed to be the best form of artificial feeding and highly recommended (Heymsfield et al. 1979; Henderson et al. 1992,1994; Moore et al. 1992; Cezard 1993; Bozzetti 1994; Duerksen et al. 1998; Jolliet et al. 1999). Nevertheless, the enteral route is not free of drawbacks, possibly related to the response of the gastrointestinal system to the administration of these diets, including discomfort, gastric distension, vomiting, nausea, diarrhea or even ulcers (Heymsfield et al. 1979; Henderson et al. 1992; Moore et al. 1992; Jolliet et al. 1999). The causes of all of these disorders have not been fully elucidated. However, some may be due to the anomalous manner in which the foods reach the digestive canal, with the absence of the cephalic phase and its neuroendocrine effects for preparing the foods and the digestive canal for the arrival and processing of the nutrients.

One approach to resolving or minimizing the problems associated with enteral nutrition may be to overcome the absence of secretions normally induced during cephalic stimulation. These problems could be addressed by subjecting the foods used to the neuroendocrine processes of the cephalic phase, as in the case of partially digested foods. This would allow nutrients to reach the gastrointestinal system in physiological conditions similar to those of normal ingestion.

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