Human Cephalic Phase Responses

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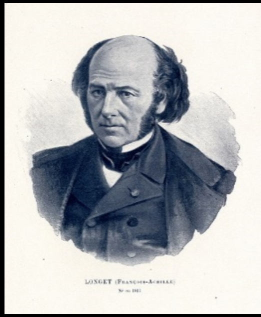
Ingestive Behavior Research Center

Cephalic Phase Responses

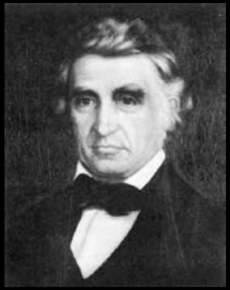
Anticipatory physiological responses driven by food cue activation of the parasympathetic nervous system with effects on ingestive behavior, digestion, nutrient absorption and metabolism

Giving Credit Where Credit is Due

“Psychic Reflexes” by Ivan Pavlov ~1890-1930



Identified and functional significance recognized by Francois Longet in 1850 (Traité De Physiologie)



Observed by William Beaumont ~1833

	Response	Magnitude	Stimulus
Appetitive	**Cravings**	+ ~30% of baseline	Sight
	Hunger	+ ~30% of baseline	Sight
Salivary	**Salivary secretion**	+~25%	Sight; Smell and taste
	Salivary IgA	-25% of baseline	Stress
Gastric	**Gastric acid secretion**	68% of pentagastrin max	MSF,Sight, smell, Cognitive
	Gastrin Secretion	~15%	MSF
	Gastric myeoelectrical activity	-30 - +10%	MSH (hotdog)
	Gastric Lipase activity	~ + 100%	MSF(chewing gum)
	Gastric emptying	-26% to -77% (cold/ hot vs body temp)	temperature
Intestinal	**Colonic pressure**	2.5-fold	Thought, smell
	GI transit time	~-23% versus control	Oral tactile
	Lipid absorption	**~5%**	**Taste**
Endocrine	**Insulin secretion**	~25%	Thought, sight, odor, taste
	Plasma adrenaline	+66% to -30%	odor
	Norepinephrine	+ 18% compared to meal feeding	MSF
	CCK secretion	~40%	MSF (liquid meal)
	Pancreatic Polypeptide	307 v -16pg/ml	Hit fat cake v control
Exocrine	**Pancreatic lipase**	2-fold	Sight, odor
	Pancreatic amylase	>100%	MSF
Circulatory	**Heart Rate**	+ ~7% of baseline	Sight
	Heart rate variability - respiratory	- ~12% of baseline	Sight
	Heart rate variability – low frequency	+ ~41% of baseline	Sight
	Diastolic blood pressure	+ ~7% of baseline	Sight
	Systolic blood pressure	+ ~8% of baseline to +230%	
	Regional Cerebral blood flow	+ 2-4% of Control	Sight
	Cardiac output	-~ 23% of baseline	Sight/smell
Cutaneous	**Skin blood flow**	+ ~8% of mineral water	Taste
	Skin conductance	+ ~28% of baseline	Sight
	Skin temperature	+ 5-10% of mineral water	Taste
	Skin resistance amplitude	+~10% of mineral water	Taste
Renal	**diuresis**	~25%	saline
	Urine osmolality	~15%	saline
Thermal	**temperature**	+ 33%(?) of baseline	Sight
	Thermogenesis	~ 42% higher with palatable stimulus	Liquid formula

Cephalic Phase Responses

- Small
- Transient
- Fragile
- Limited consequence

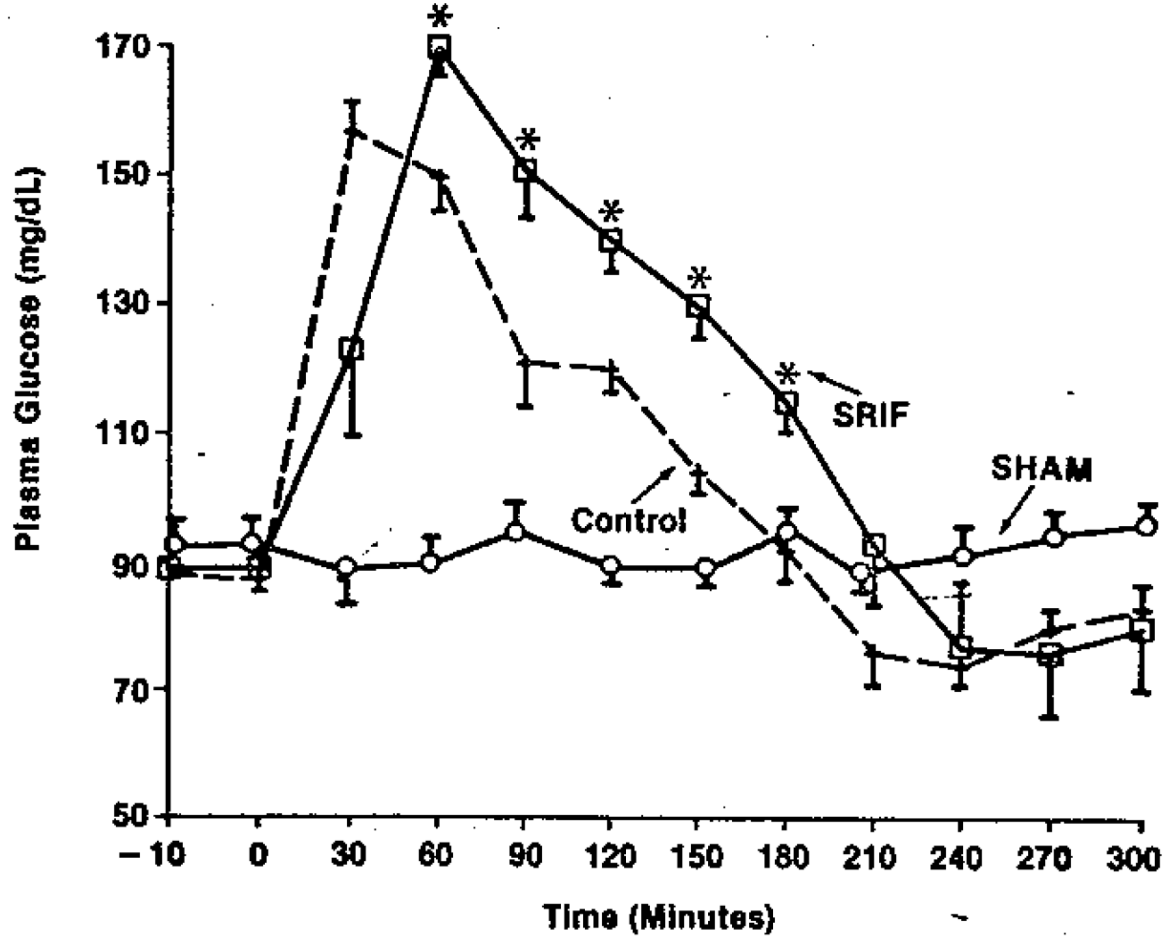
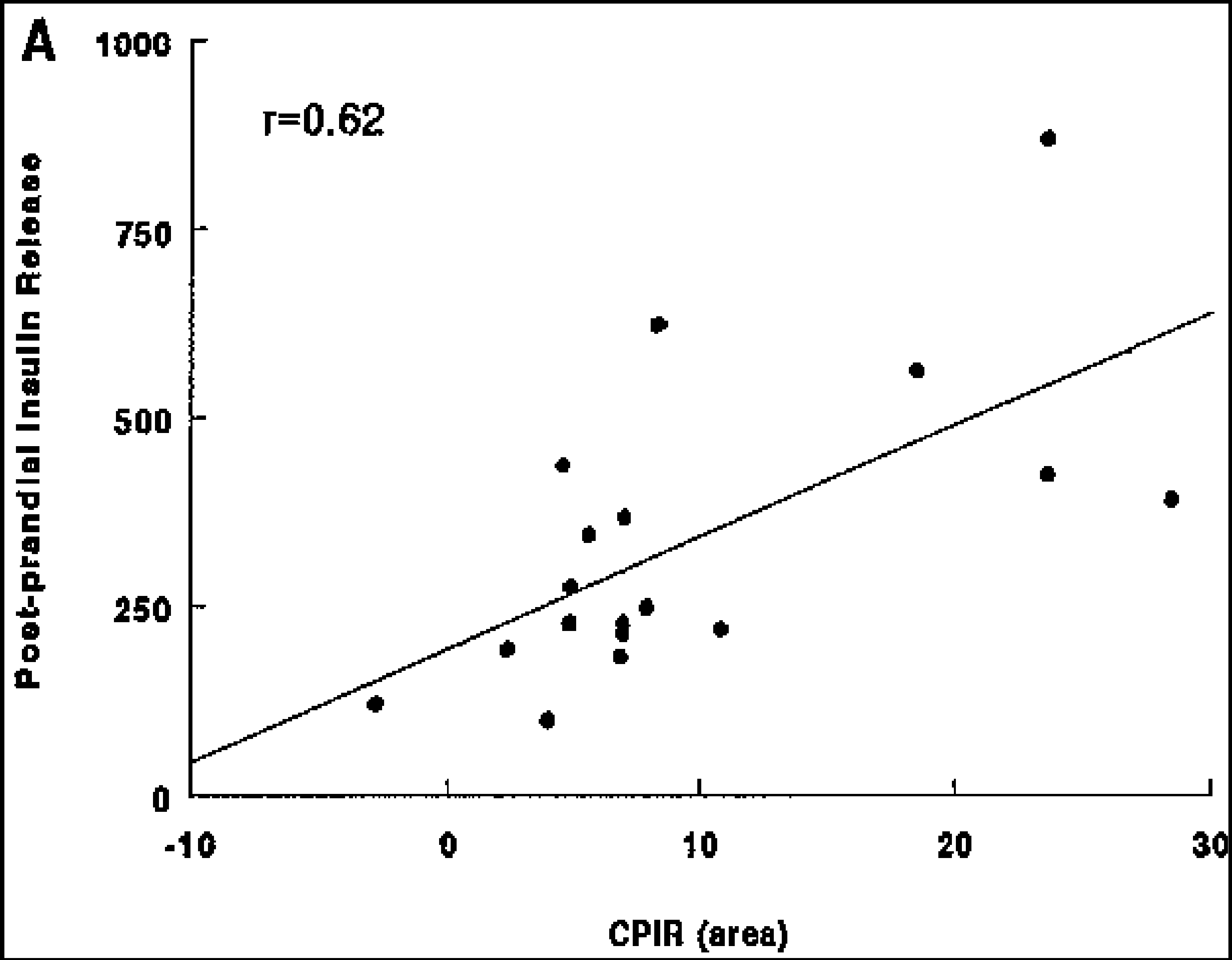


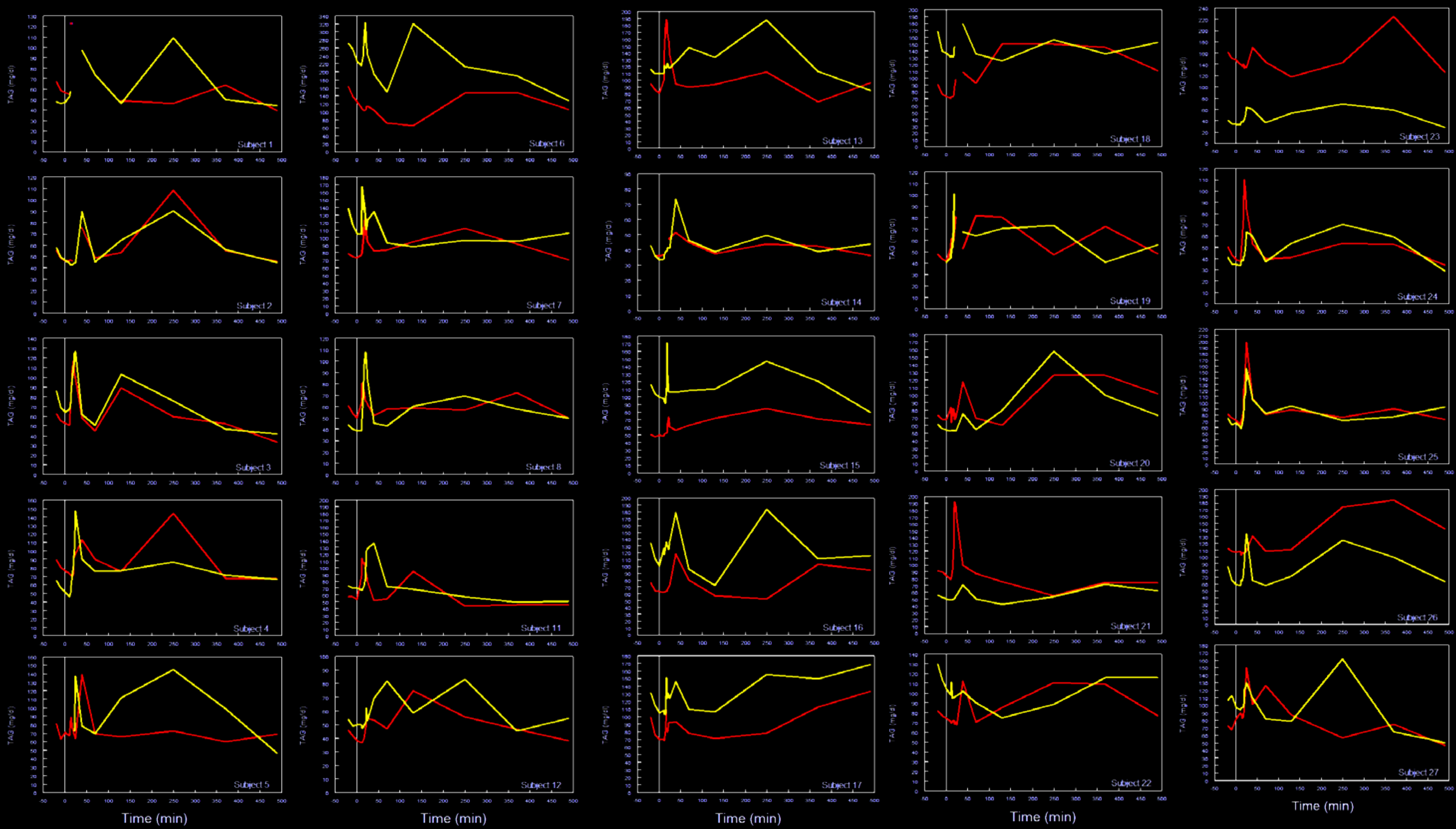
FIG. 3. Oral glucose tolerance test (OGTT) showing plasma glucose response. There was deterioration of glucose tolerance associated with loss of early phase of insulin release; no episode of reactive hypoglycemia was observed. There was no difference in total amount of carbohydrate oxidized, suggesting that nonoxidative disposal of glucose was responsible for this deterioration. *$P < .05$ vs. control.

Escandon-Calles J, Robbins DC. Diabetes 1987; 36:1167.

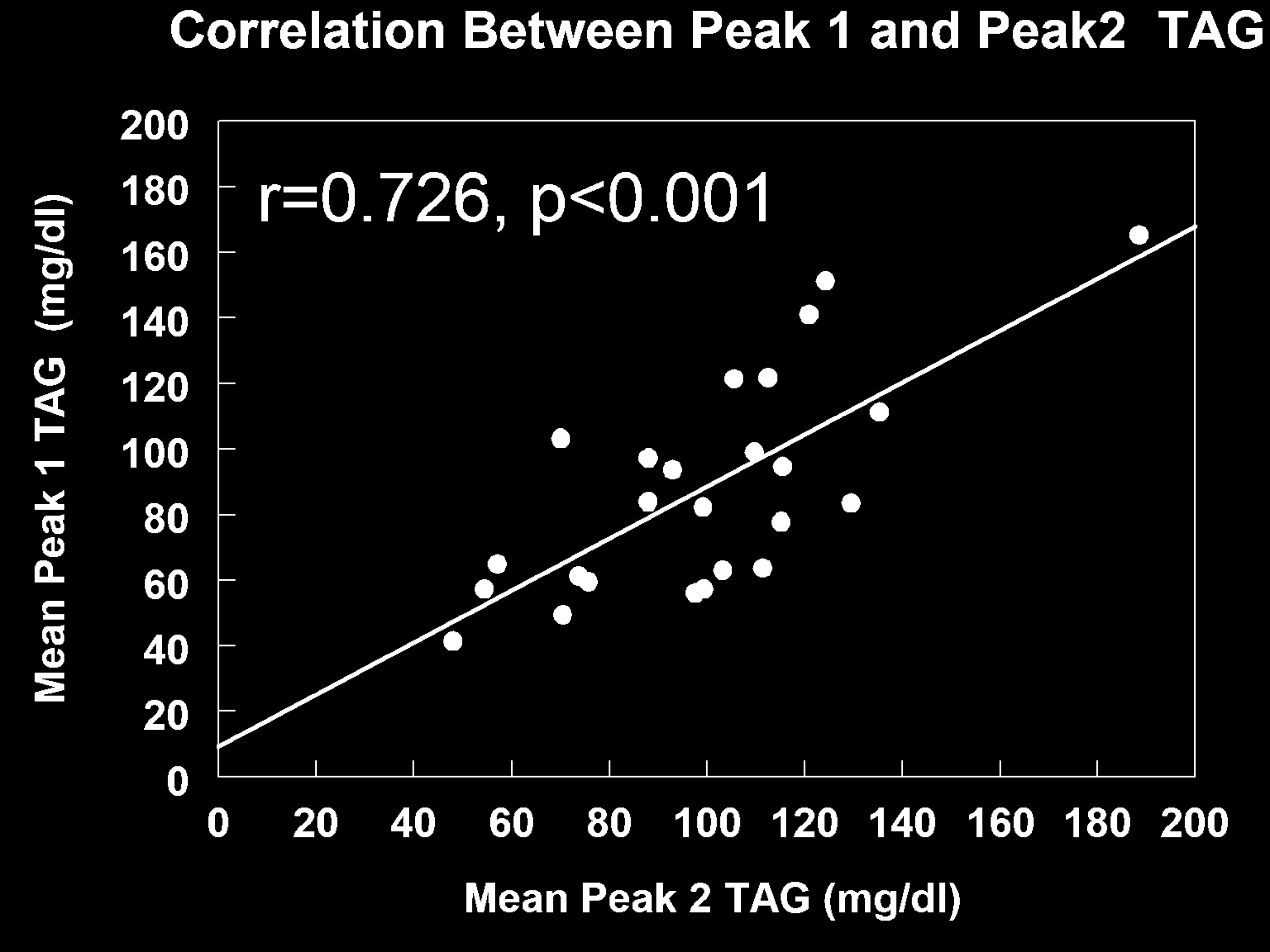


Teff et al., 1993;42:1600-1608

Without Oral Fat Stimulation/With Oral Fat Stimulation



Mattes RD. J Nutr 2002; 132: 3656-3662.


Correlation Between Peak 1 and Peak2 TAG
r=0.726, p<0.001
Mean Peak 1 TAG (mg/dl)
Mean Peak 2 TAG (mg/dl)
0
20
40
60
80
100
120
140
160
180
200

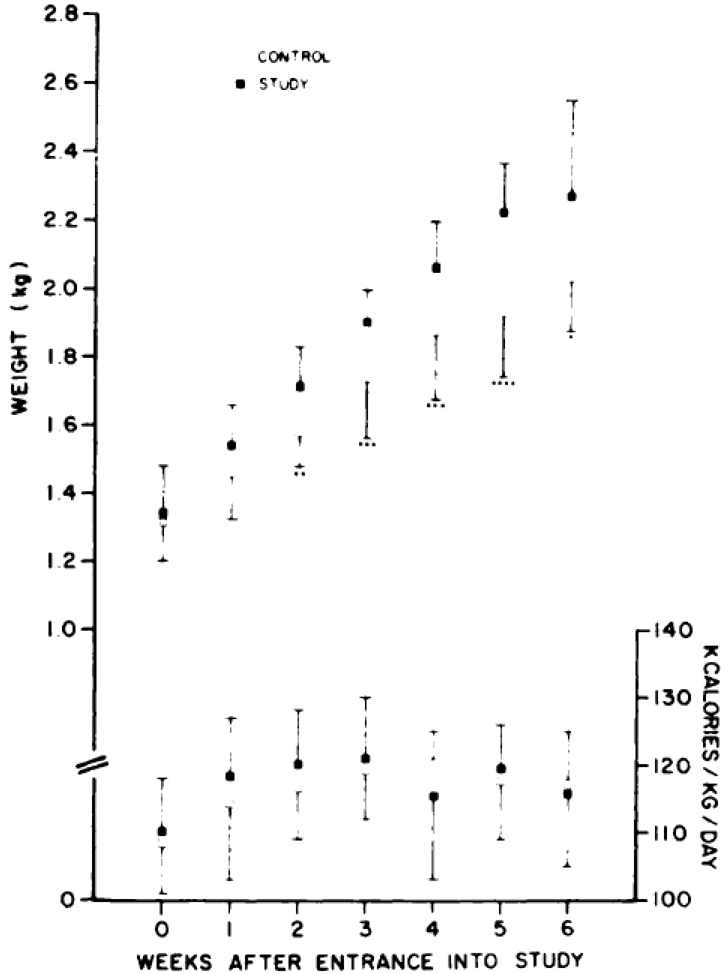


Fig 1. Weight compared to caloric intake. Upper graph shows comparative weekly weights (means ± 1 SD) which become and remain significantly different by second week after entrance (one asterisk, $P < .05$; two asterisks, $P < .02$; three asterisks, $P < .01$; four asterisks, $P < .001$). Lower graph shows no significant differences in caloric intake throughout study period.

Bernbaum et al., Pediatr 1983;71:41-45

Effective Stimuli

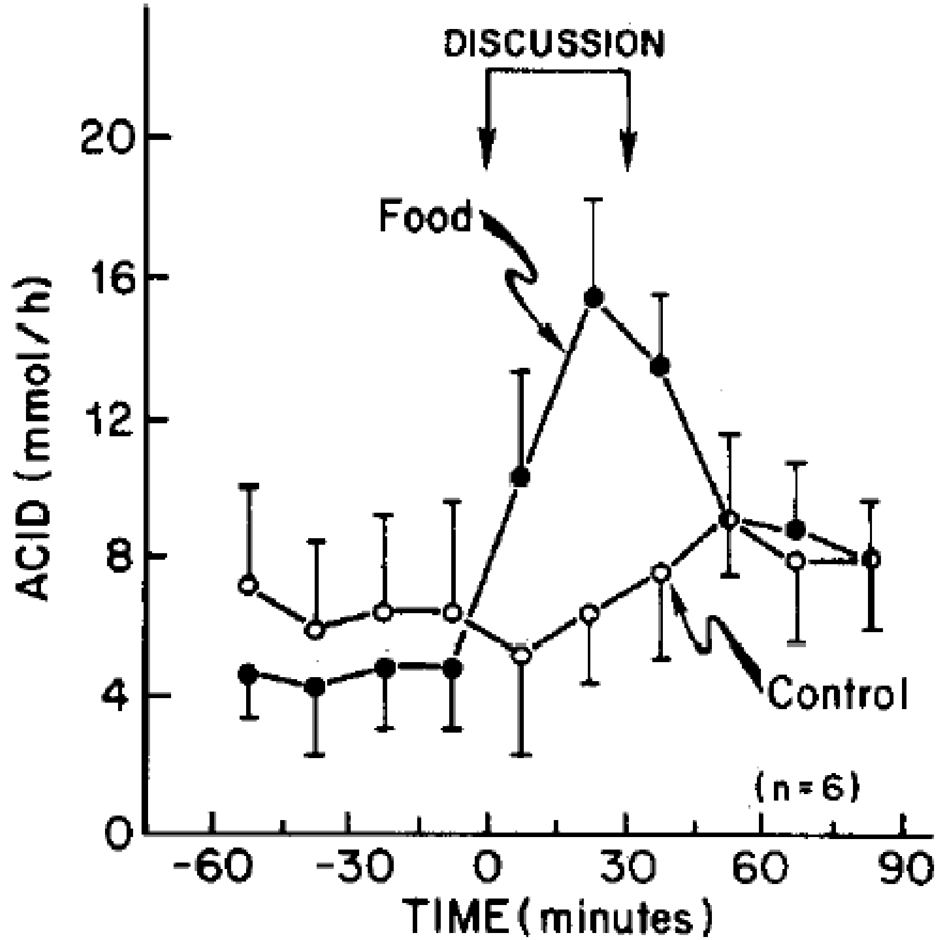


Figure 3. Effect on mean (±SEM) gastric acid output of a 30-min discussion about food or about topics other than food (control) in 6 subjects. Food discussion increased acid secretion significantly, whereas the control discussion did not.

Feldman & Richardson Gastroenterol 1986;90:428-433

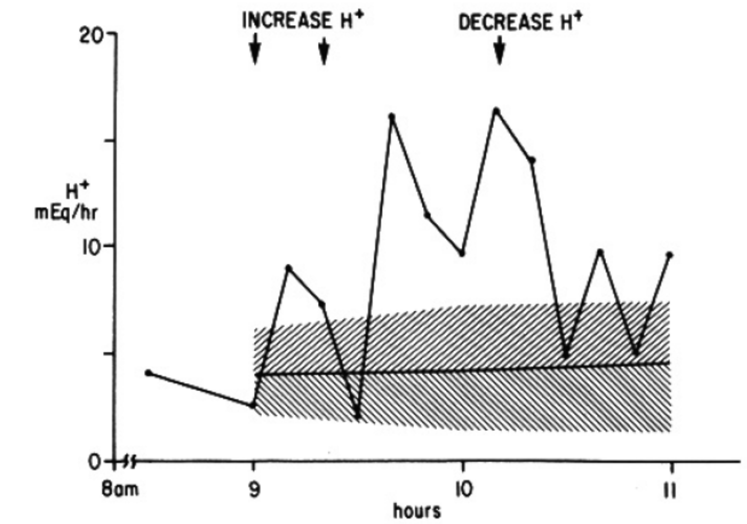


FIG. 4. Interview session with biofeedback. *Heavy line* and *shading* indicates control secretion. *Arrows* denote instructions to increase or decrease acid output. Subject was successful in 11 of 12 10-min trials.

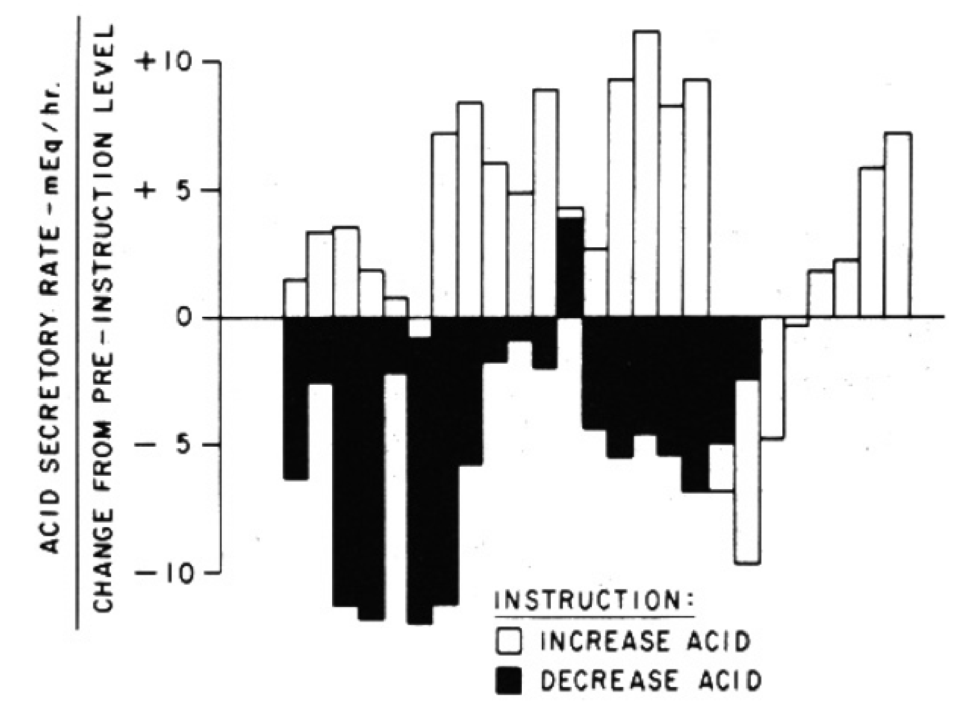
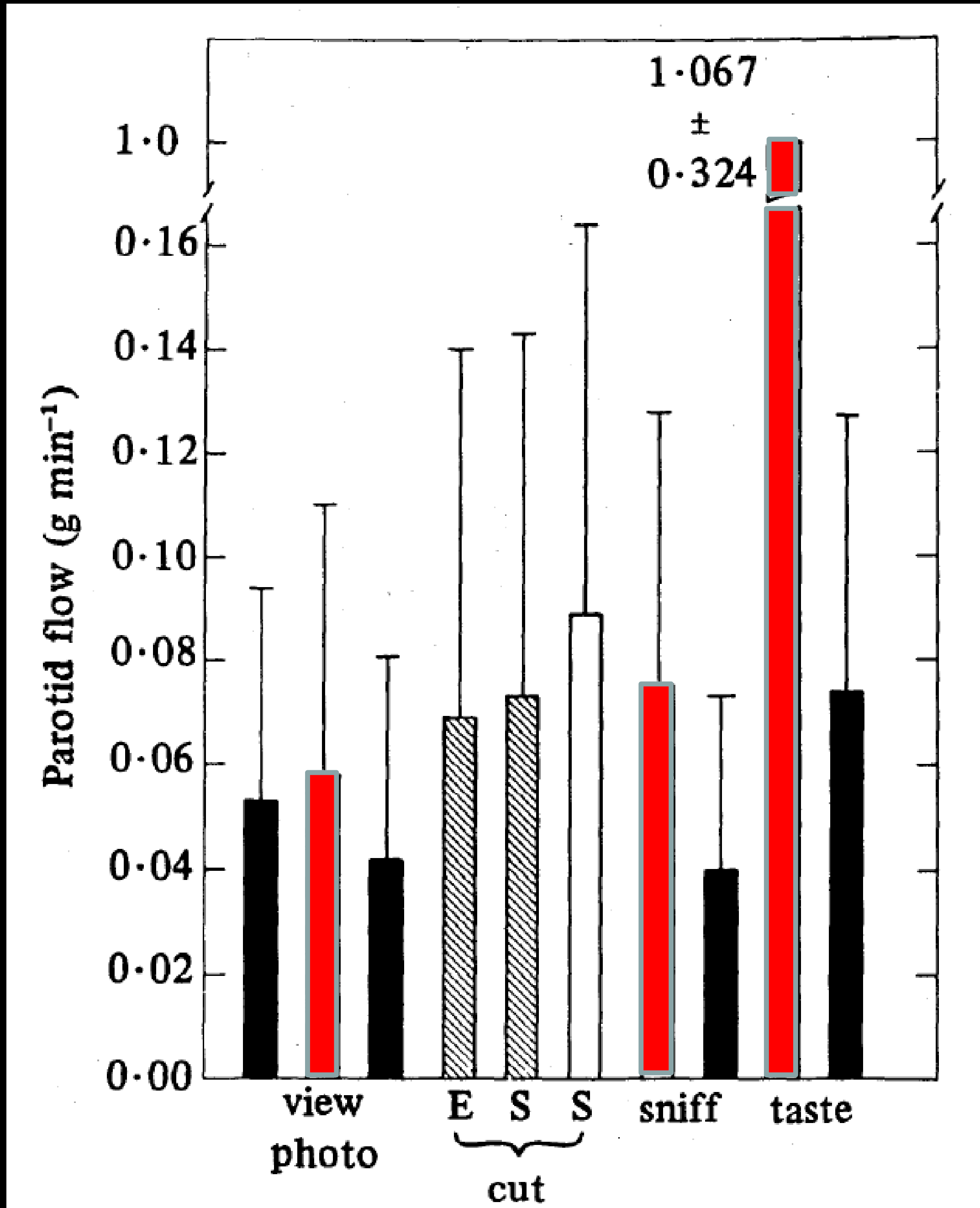


FIG. 5. Biofeedback training summary. Forty-four 10-min samples following 14 instructions to decrease or increase acid secretion in four interview sessions. *Open bars* represent results following instructions to increase acid; *closed bars* represent results following instructions to decrease acid. Each sample is compared with the preinstruction secretory level. Correct responses are *open bars* above and *closed bars* below the preinstruction secretory level ("0"). Thirty-eight responses were correct; six were incorrect.

Moore & Schenkenberg Gastroenterol 1974;66:954-959



Pangborn et al., Perception 1979;8:339-346

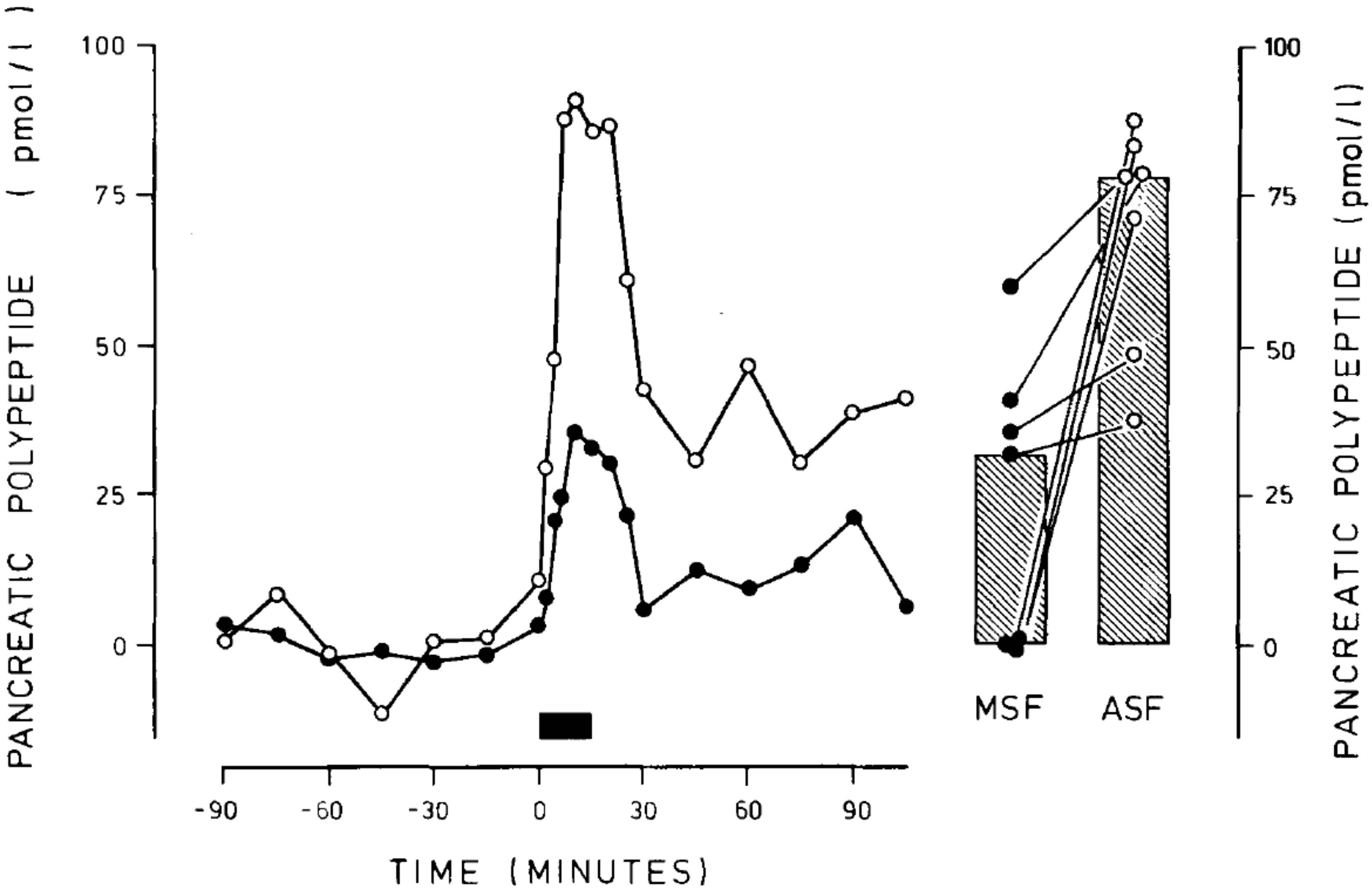


Fig. 4. The effect of adequate sham feeding (○——○, and ASF) and modified sham feeding, 'chew and spit' (●——●, and *MSF*), indicated by bar, on plasma concentrations of pancreatic-polypeptide (increments) in 7 duodenal ulcer patients. Columns to the right indicate the median integrated PP response shown as ideal mean concentration from 0 to 30 min (integrated response divided by 30 min).

Schwartz et al., Scand J Gastroent 1979;14:313-320

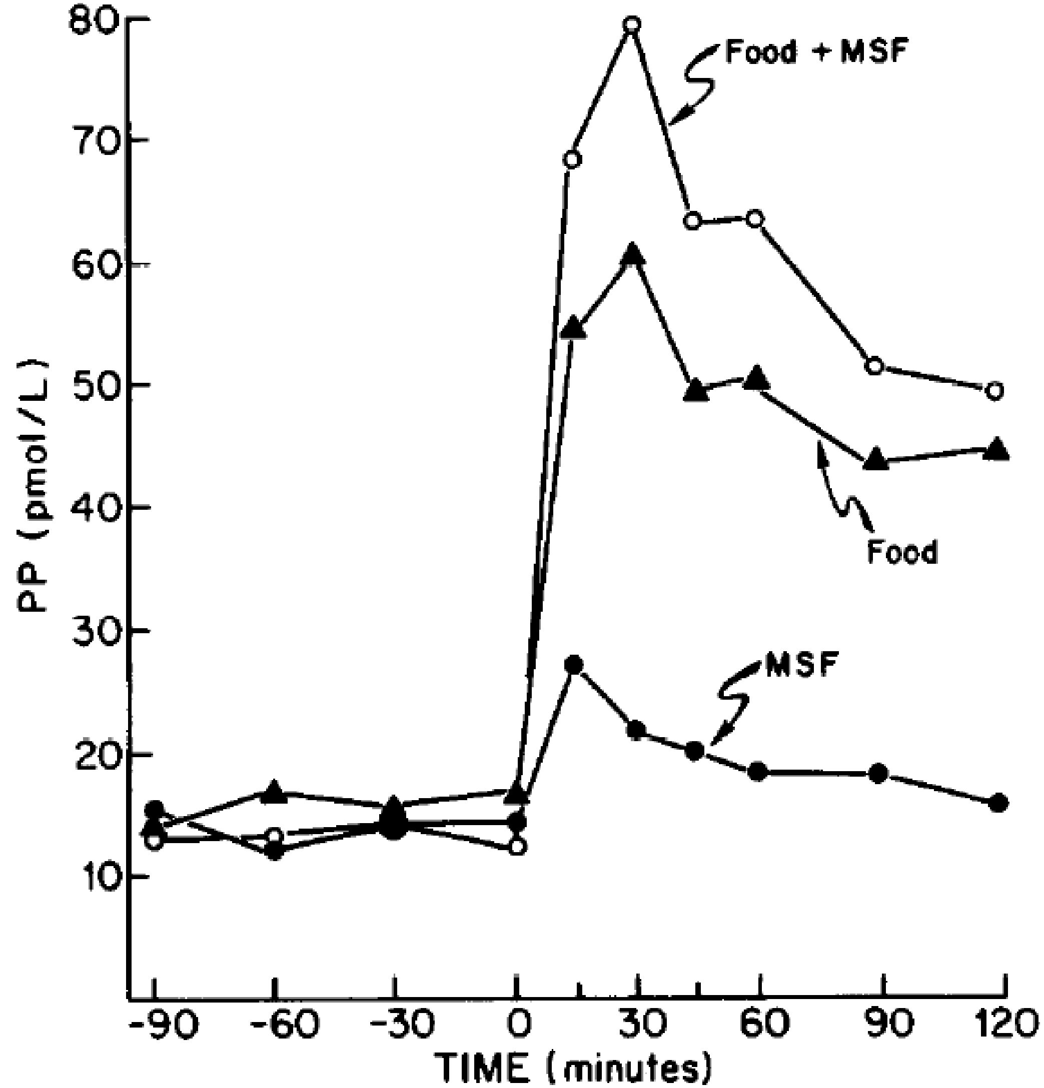


FIG. 3. Mean pancreatic polypeptide (*PP*) responses to modified sham feeding (*MSF*), intragastric food, and intragastric food plus MSF in 6 normal subjects. MSF was begun and/or food infused into the stomach at 0 min.

Taylor et al., Gastroenterol 1978;75:432-437

Stimulus Summary

- Any food cue can may be effective

Swallowing>masticating>taste>odor>appearance>thought

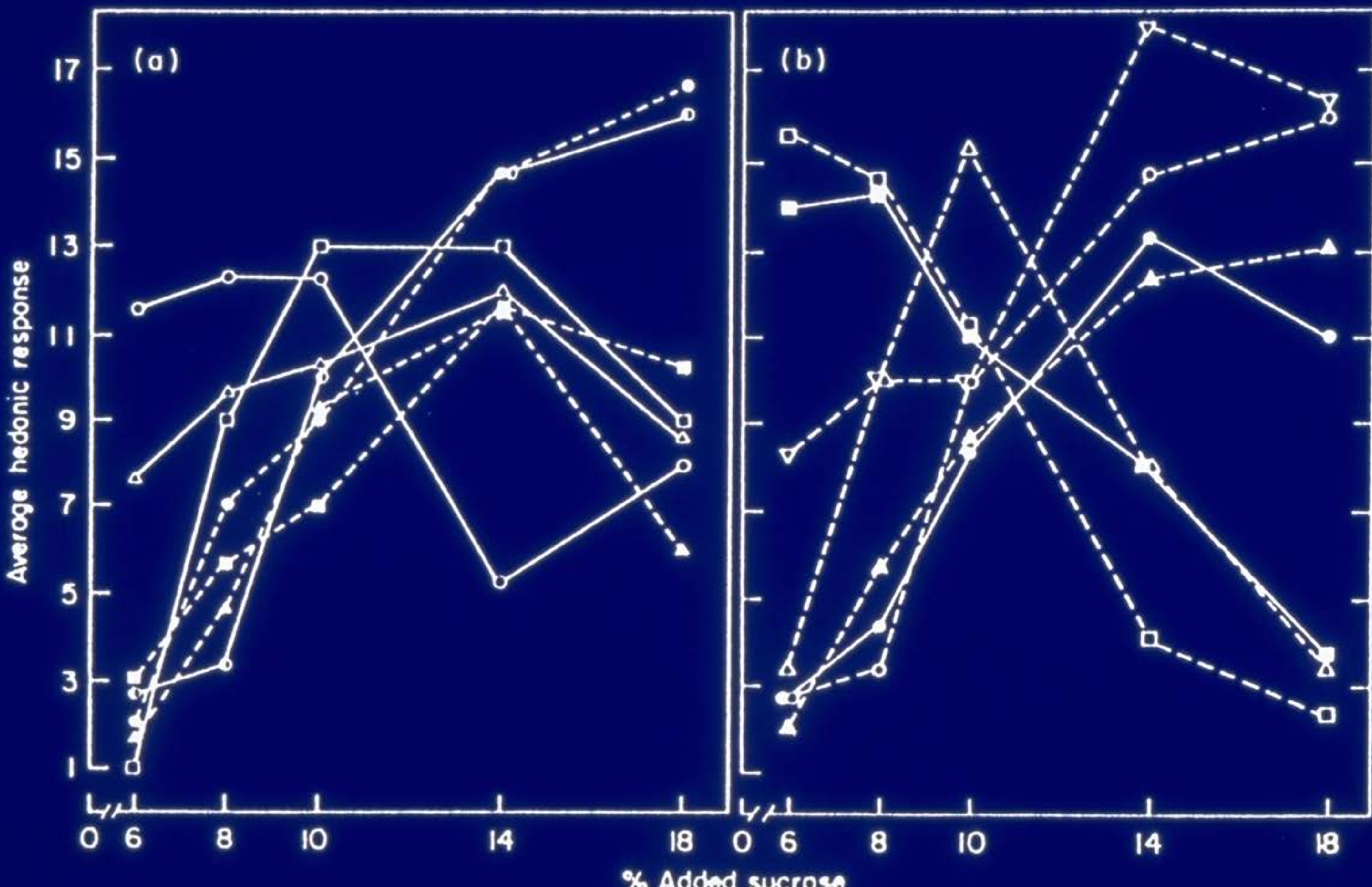


FIGURE 1. Individual hedonic responses from seven normal (a) and seven obese (b) subjects to sweetness in lemonade. Each point is the average of three judgments on a scale where 1 = dislike extremely, and 17 = like extremely.

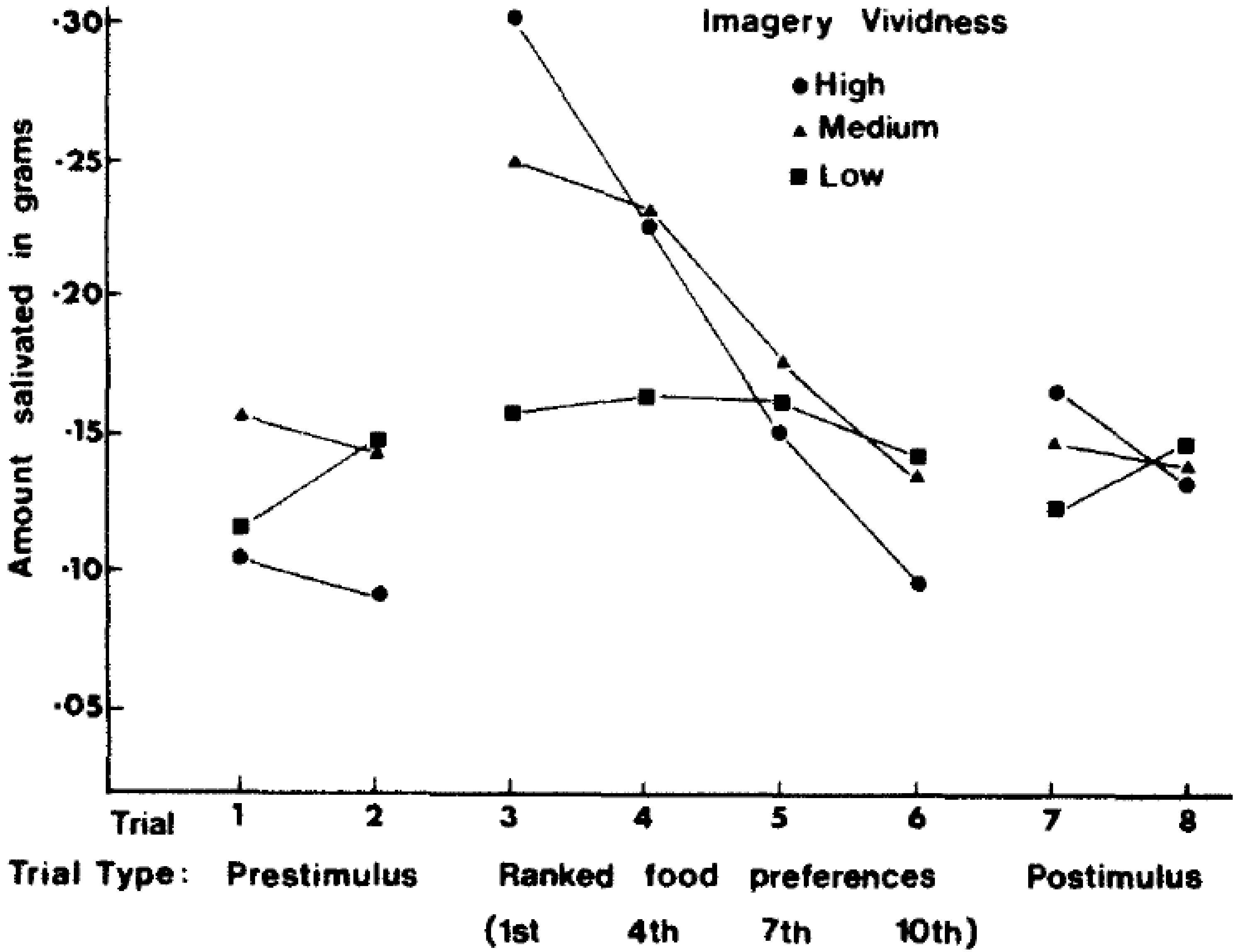
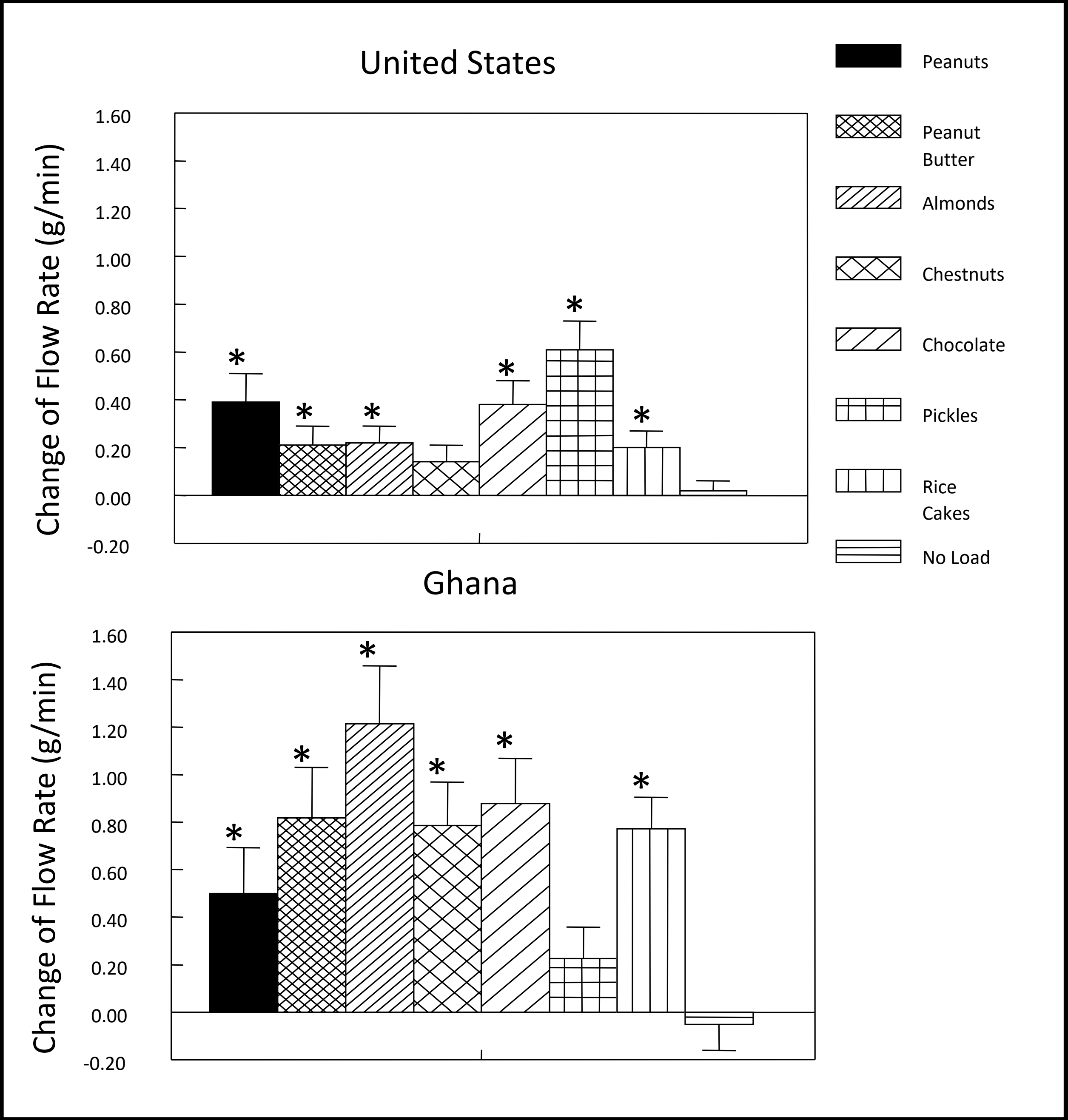
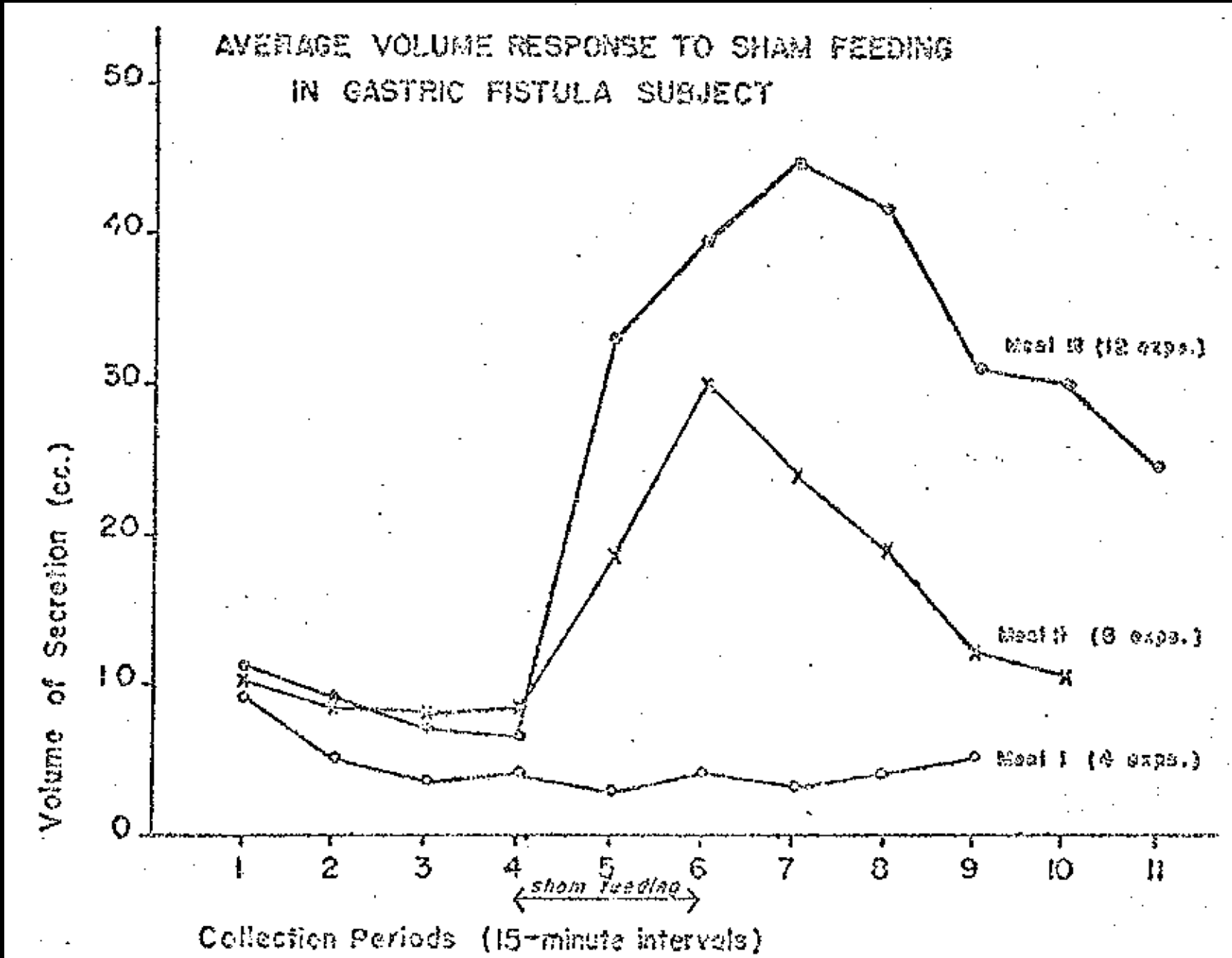


Fig. 2. Amount salivated by each imagery group on each trial.

White KD Psychophysiology 1978;15:196-203



Lokko et al., Fd Qual Pref 2004;15:129-136



Janowitz, H.D., et al. Gastroenterology 16(1):104, 1950.

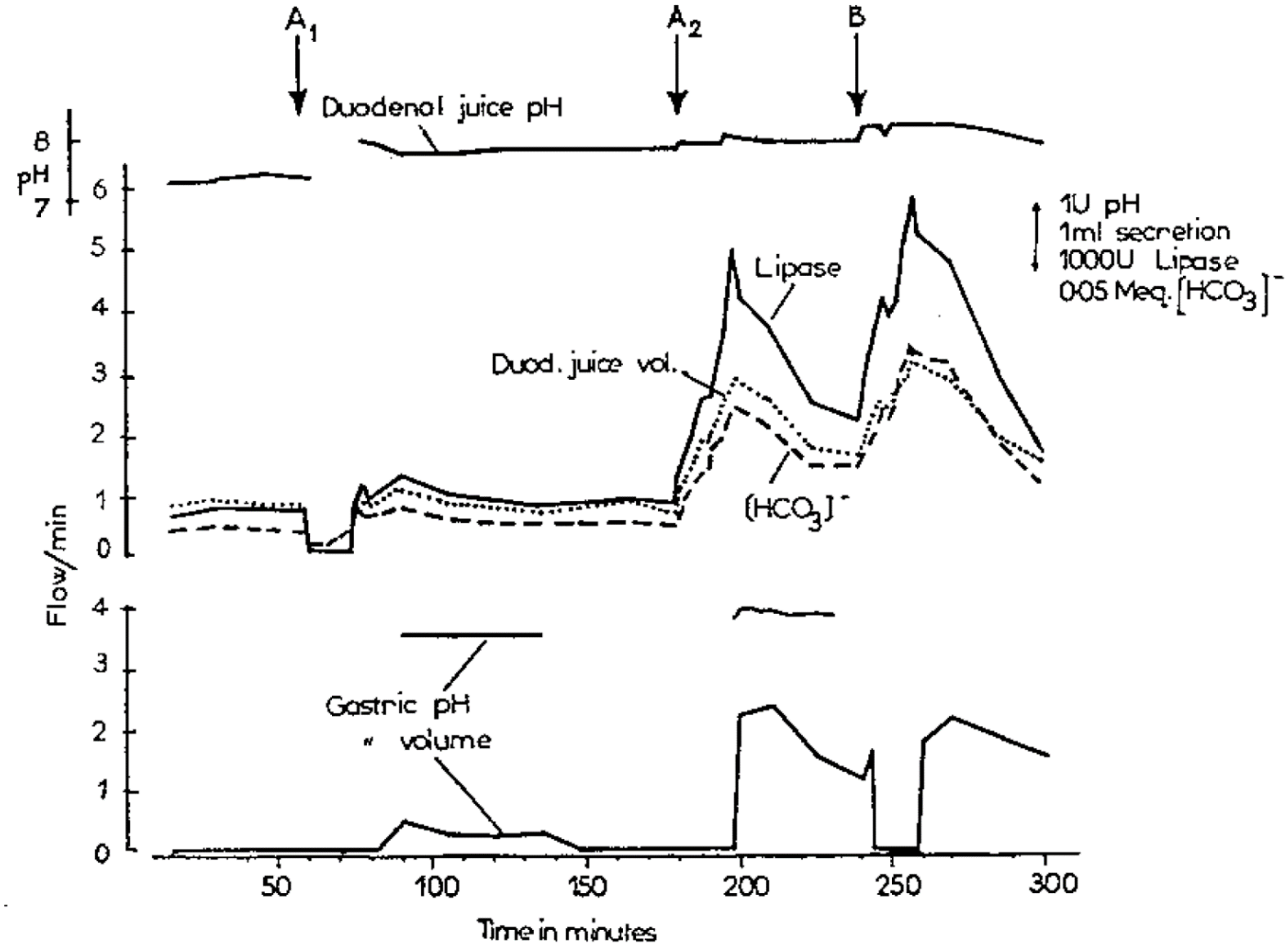


FIG. 1. *Response to early and late type A psychic stimulation and of type B sham feeding.*

Sarles et al., Gut 1968; 9:214

Cephalic phase of pancreatic secretion in man

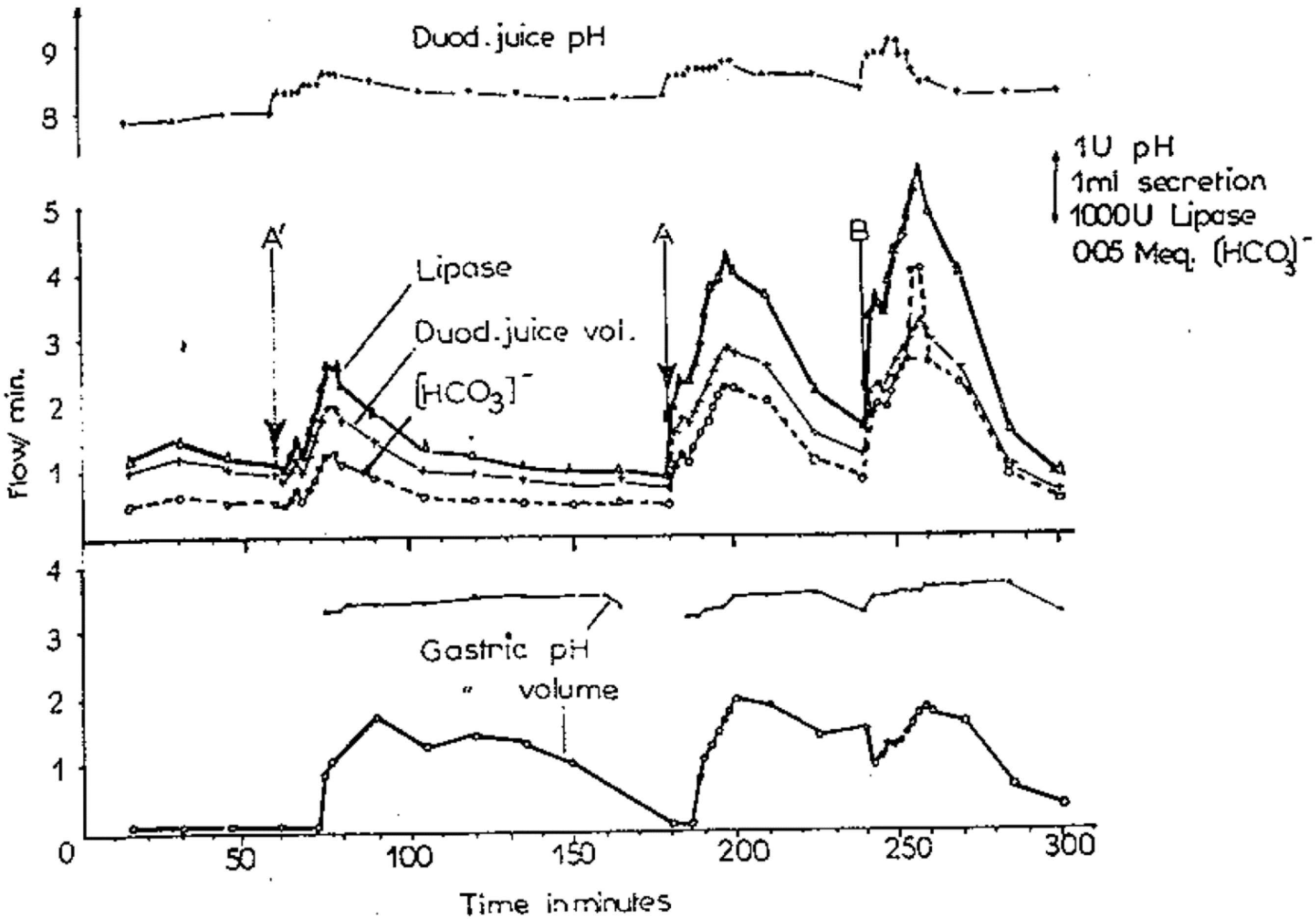


FIG. 2. *An experiment similar to that in Figure 1, except that type A*[1] *replaces type A stimulation at 8.30 a.m.*

Sarles et al., Gut 1968; 9:214

Stimulus Summary

- Any food cue can may be effective

Swallowing>masticating>taste>odor>appearance>thought

- Palatability enhances the magnitude of responses

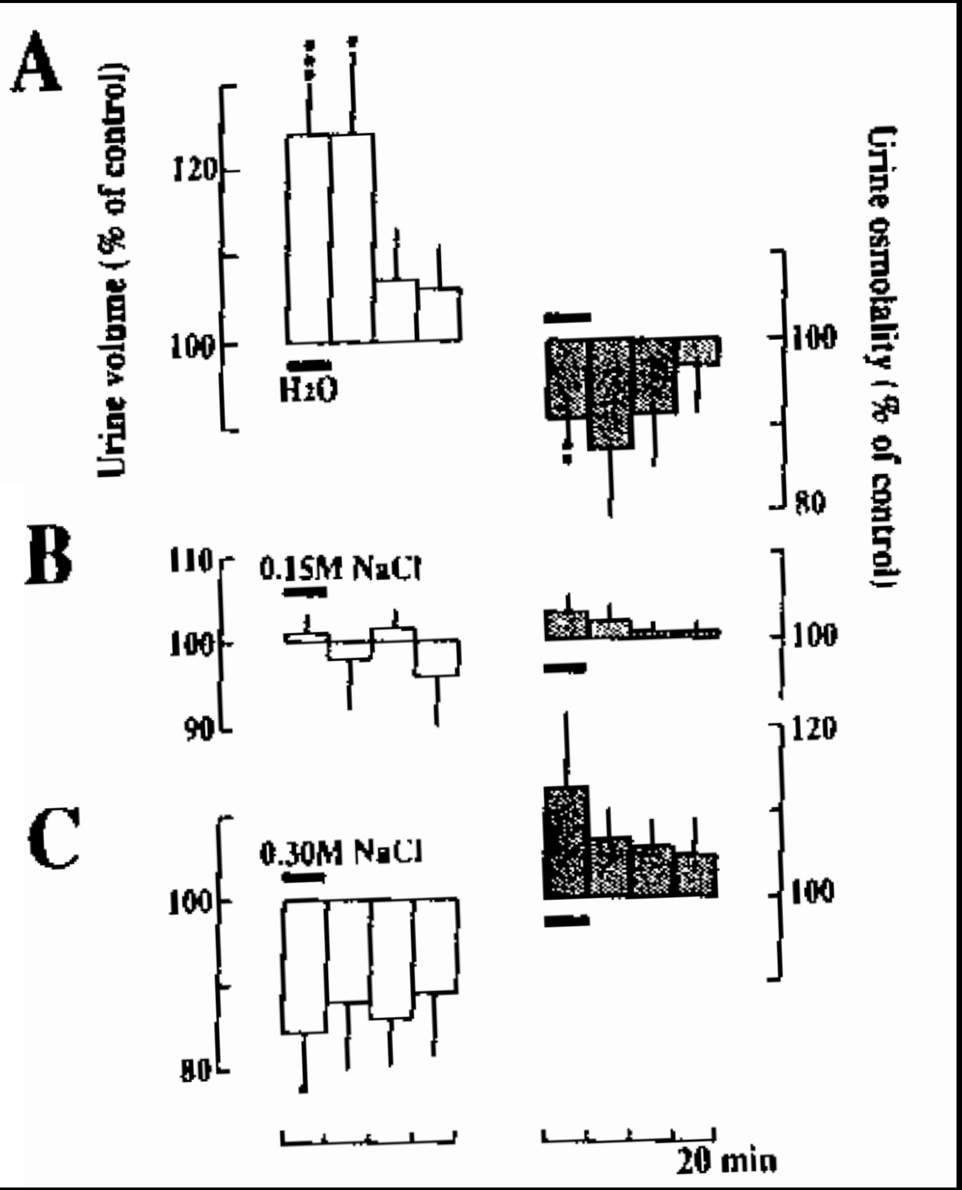
Palatability is determined by more than sensory properties

Cephalic Phase Responses

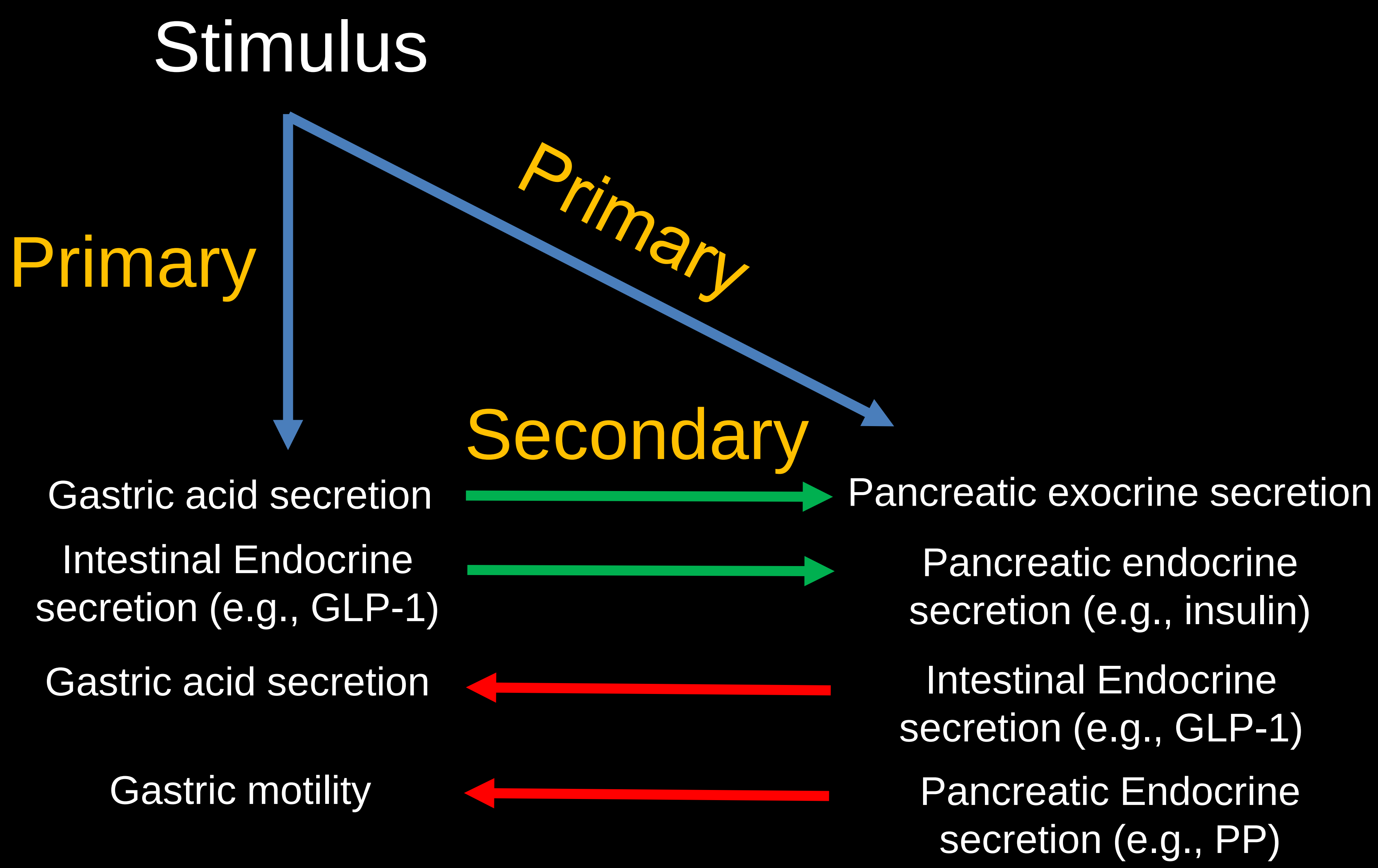
Function:

Optimization of Nutritional Status

Metabolic Regulation



Akaishi et al., Chem Senses 1991; 16:277-281

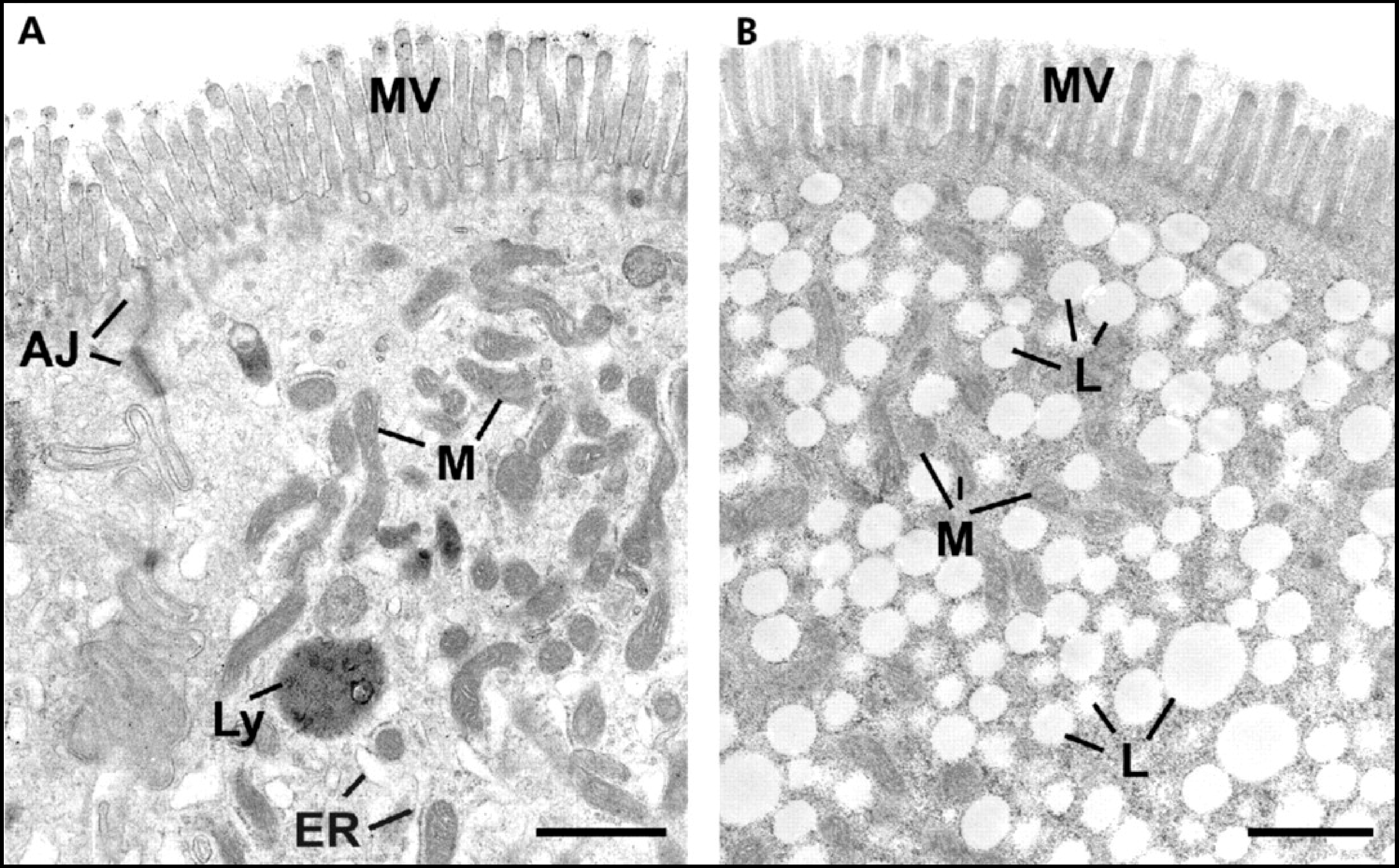

Stimulus
Primary
Primary
Secondary
Gastric acid secretion
Pancreatic exocrine secretion
Intestinal Endocrine secretion (e.g., GLP-1)
Pancreatic endocrine secretion (e.g., insulin)
Gastric acid secretion
Intestinal Endocrine secretion (e.g., GLP-1)
Gastric motility
Pancreatic Endocrine secretion (e.g., PP)

Cephalic Phase Responses

Function:

Optimization of Nutritional Status

- **Metabolic Regulation**
- **Facilitation/Accommodation**



MV = microvilli   AJ = apical juctional complex   ER = endoplasmic reticulum
M = mitochondria   LY = lysosome

Robertson, M D et al. Gut 2003;52:834-839

Cephalic Phase Responses

Function:

Optimization of Nutritional Status

- **Metabolic Regulation**
- **Facilitation/Accommodation**
- **Behavioral Regulation**

Cephalic Phase Insulin Response

REF	N	Draw Timing Post Exposure	Stimuli
Teff et al 1993	18 NW 15 OB	2, 4, 6, 8, 10, 12, 14	MSF mousse
Simon et al. 1986	10NW 15 OW	Every min for 16 min	Visual and olfactory – meal
Sjostrom et al., 1980	23NWF 25 OBF	1, 2, 3, 4, 5, 6, 10, 15 ,20	Visual an Olfactory - meal
Para Covarrubias 1971	6	5, 10, 15, 20, 25, 30, 45, 60	Visual and odor
Sahakian et al., 1981	14NW	2, 4, 6, 10 min	Visual and Olfactory
Johnson Wildman 1983	6NW 4OB	2.5, 5, 7.5,10, 20	Imagined; visual and olfactory
Teff 1995	31 NWM	1, 3, 5, 7, 9, 11, 13, 15 20, 25, 30	Solutions and MSF
Macourek et al., 2013	15 NWM	5, 10, 15, 20 min	Sucrose aspartame, water
Just et al., 2008	20NW	3, 5, 7, 10 min	Sucrose, saccharin, acetic acid, NaCl, QHCl, Water
Bellisle et al., 1987	2NWW 3NWM	Every minute	Sandwich (high and low
Bellisle et al., 1983	4 NWW, 3NWM	I min for 30 min then 3 min intervals	Sandwich
Bellisle et al., 1985	6NW 4NWM	1 min intervals	Sandwich (high and low palatability
Teff 1996;	13 NWW	2, 4, 6, 8, 10, 12, 14, 16, 21, 26, 31	Palatable and unpalatable food
Teff 1991	20 NWM	2, 4, 6, 8, 10, 21, 2612, 14 ,16	ASP in mousse
Yamazaki 1986	57NWM	1, 2, 3, 4, 5, 6, 7, 8, 9, 10	glucose
Bruce 1987	6NW 7NW 5NW	1, 2, 3, 4, 5	Visual and Odor; taste
Osuna et al 1986 see Morricone	5NW 10Ob	1, 2, 3, 4, 5	Visual an odor

REF	N	Draw Timing Post Exposure	Stimuli
Ford et al., 2011	8NW	0, 2, 4, 6, 8, 10	Sucralose in water
Goldfine et al.,	7NWM	4, 8, 12, 16, 20, 24, 28, 32	hypnosis
Taylor et al 1982	7NW	0, 15, 30,45, 60, 90,120	Sham-fed meal
Veedfeld et al., 2015	10 NWM	0, 2, 4, 6, 8, 10, 12, 17	MSF
Bello et al., 2010	10 HW and 10 women with bulemia	2, 4, 6, 8, 10, 12, 14, 19, 24, 29	MSF choc dairy bev
Marricone et al. 1999	Study 1: 12 NW and 12OB Study 2: 5 OB N=6 sacc N=6 lemon	0, 1, 2, 3, 4, 5, 10, 20, 50	Study 1: Water, saccharin, lemon juice Study 2: combined with visual and/or olfactory stimulation
Abdallah 1997	12 NWM	1 min intervals	Sucrose, aspartame, polydextrose Tablets
Kurhunen et al 1996	11ObW Binge-eating 10ObW non-binge-eating	1, 5, 7.5, 8, 11, 13.5,14, 15.5,18, 20.5,21, 24, 25	Cognitive/visual & odor/ MSF

Responders
vs.
Non-Responders

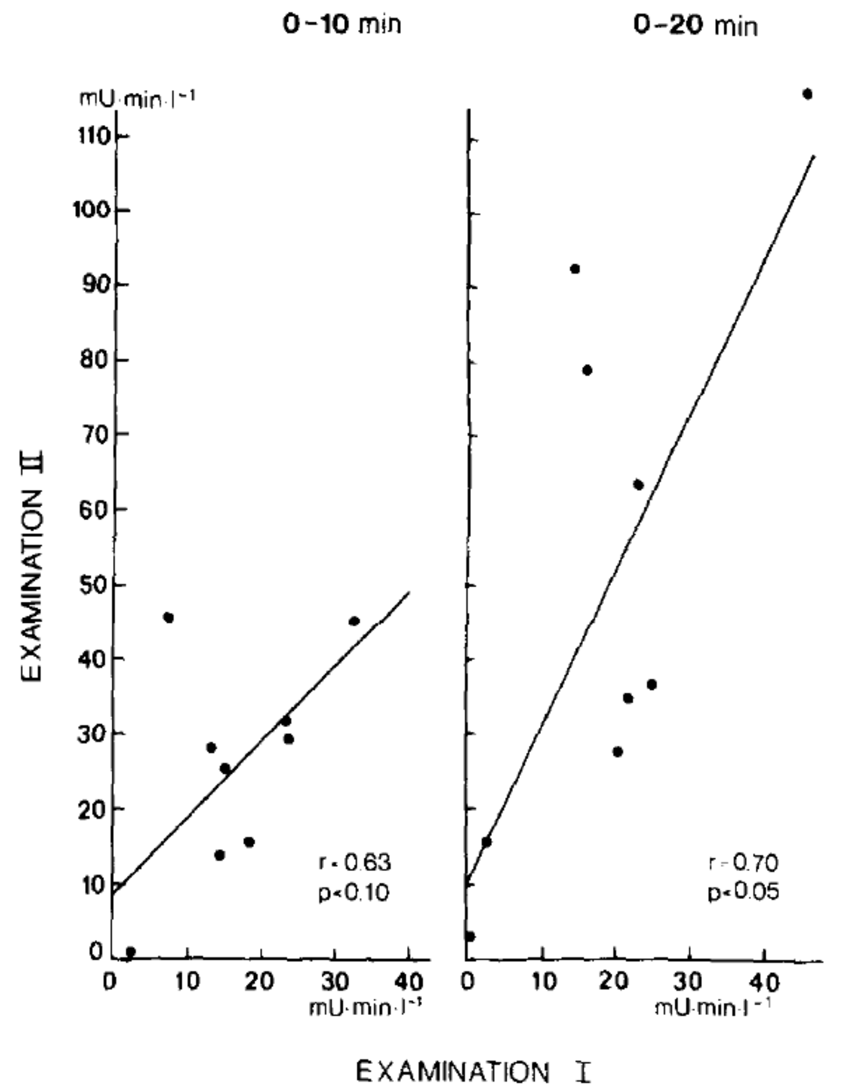
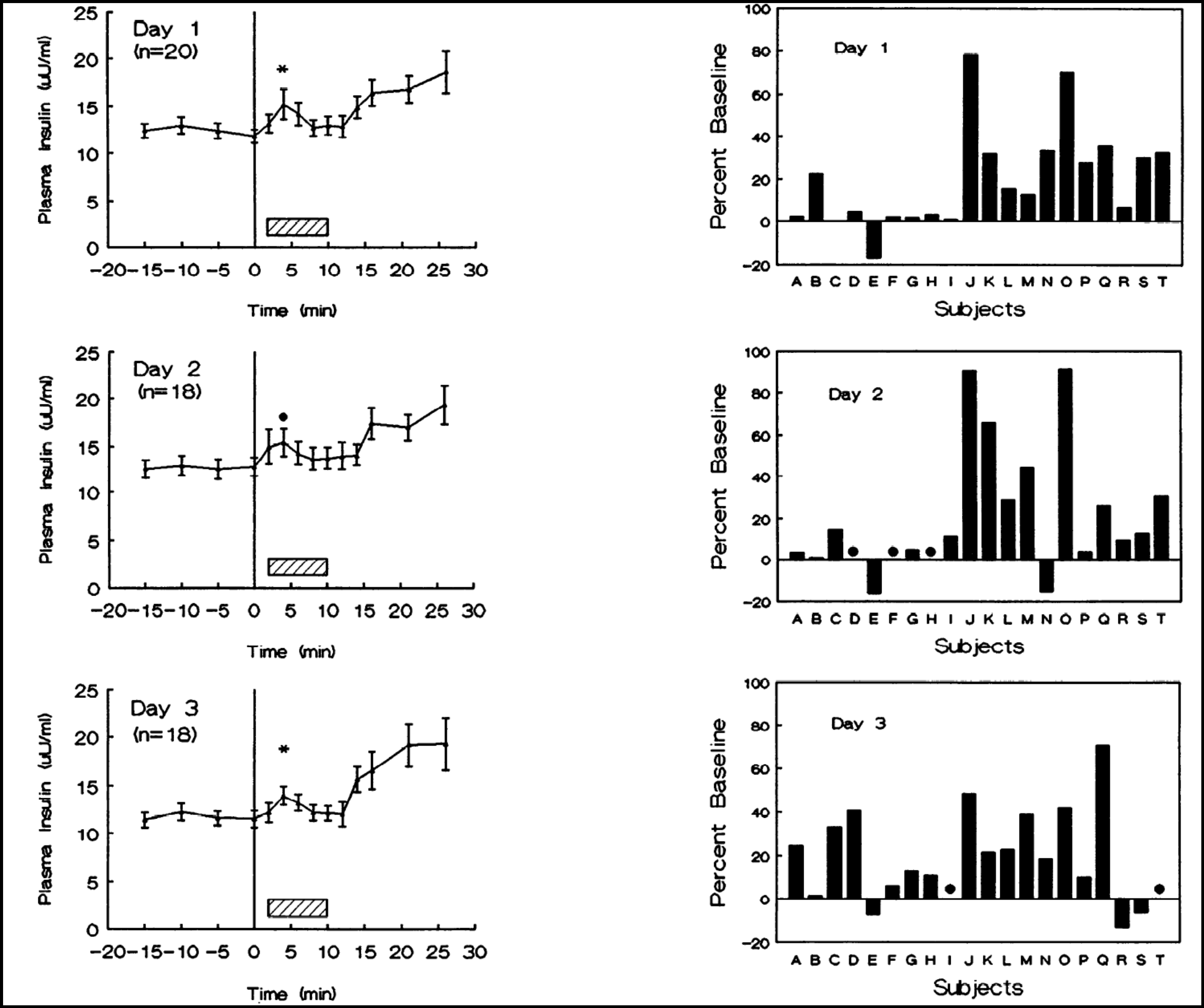


Fig. 2. Correlations between insulin areas (method II) during the sight and smell of food in two consecutive examinations of nine obese subjects. Calculations on areas during 0–10 and 0–20 min after start of food presentation are shown in the left and right panel, respectively.

Sjostrom et al Metab Clin & Exp 1980;29:901-909



Teff et al., Am J Physiol 1991;261:E430-E436

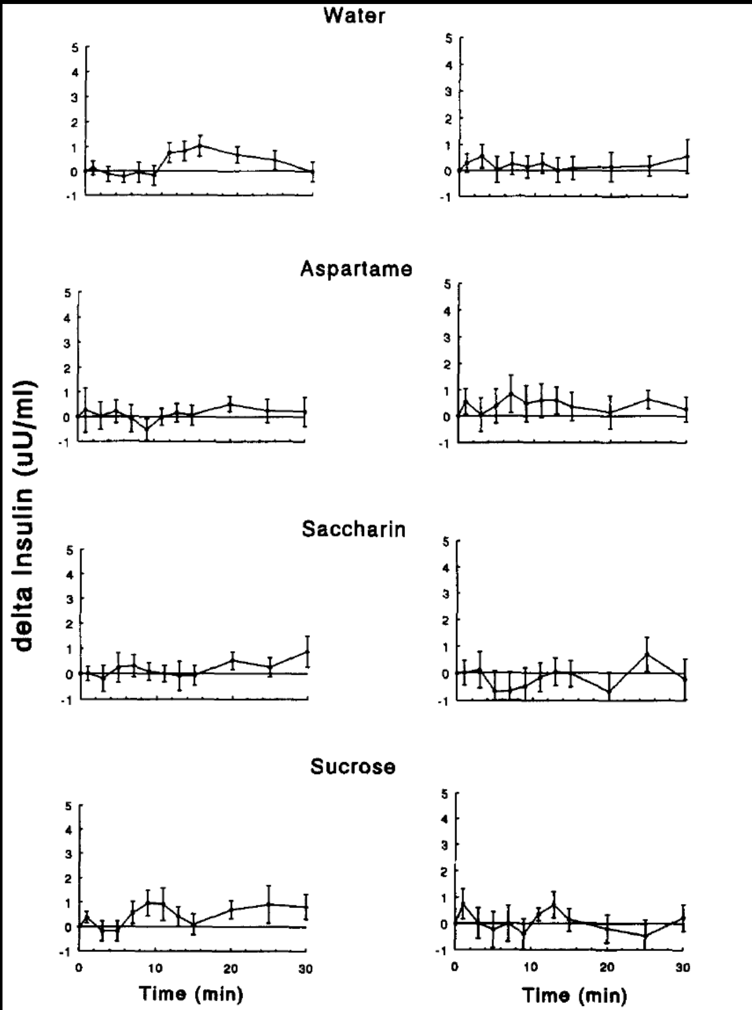


FIG. 1. Mean ± SEM changes in plasma insulin from baseline (delta insulin) after subjects sipped and spit solutions for a 1-min period (graphs in left column; n = 15) and a 3-min period (graphs in right column, n = 16). No statistically significant changes in plasma insulin were found.

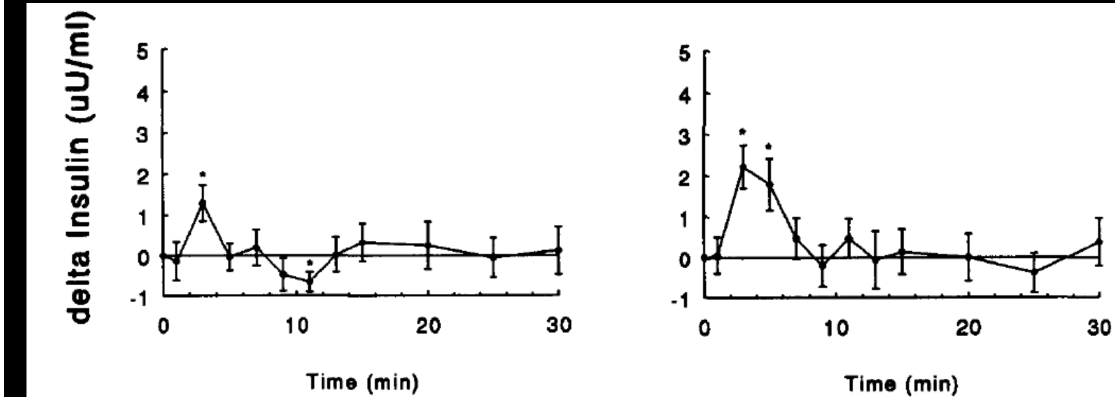


FIG. 2. Mean ± SEM changes in plasma insulin from baseline (delta insulin) after subjects sham-fed apple pie for a 1-min period (left graph, n = 15) and a 3-min period (right graph, n = 16). *indicates statistically significant differences from baseline mean (mean of four pretreatment values), $p < 0.05$.

Teff et al.,Physiol & Behav 1995;57:1089-1095

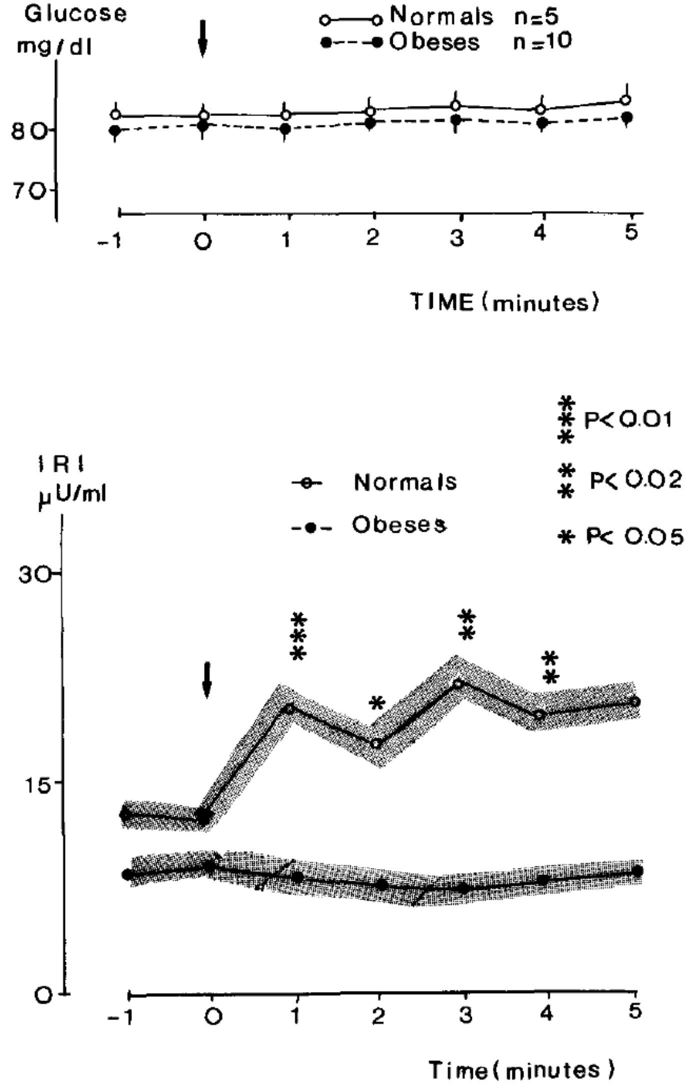


Fig. 3 Glycemia and insulinaemia values in normal female volunteers and obese female patients during visual stimulation of the cephalic phase of reflex insulin secretion (average ± SME).

Osuna et al, Horm Metbol Res 1986;18:473-475

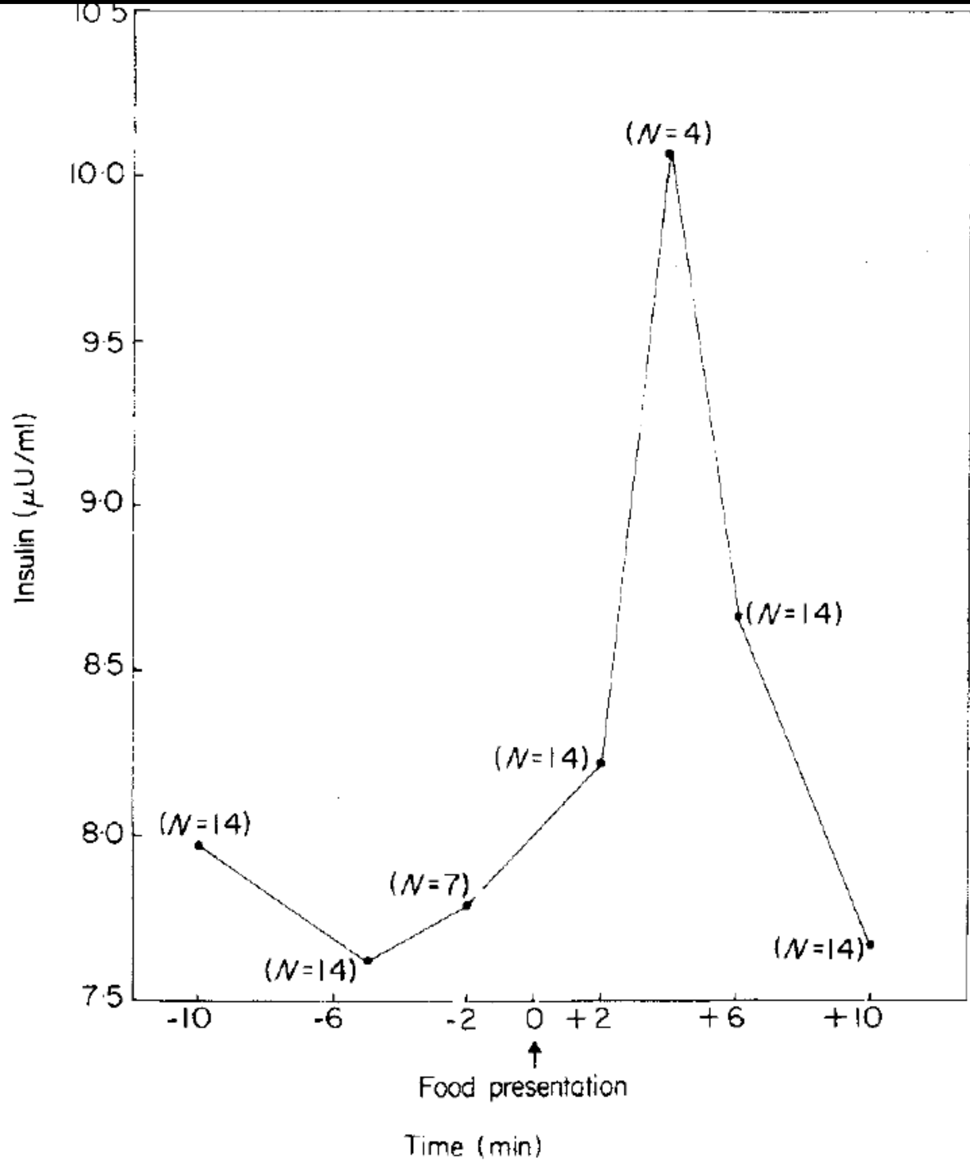


FIGURE 1. Plasma insulin concentrations (means) at different times before and after presentation of food.

Sahakian et al., Appetite 1981;2:209-216

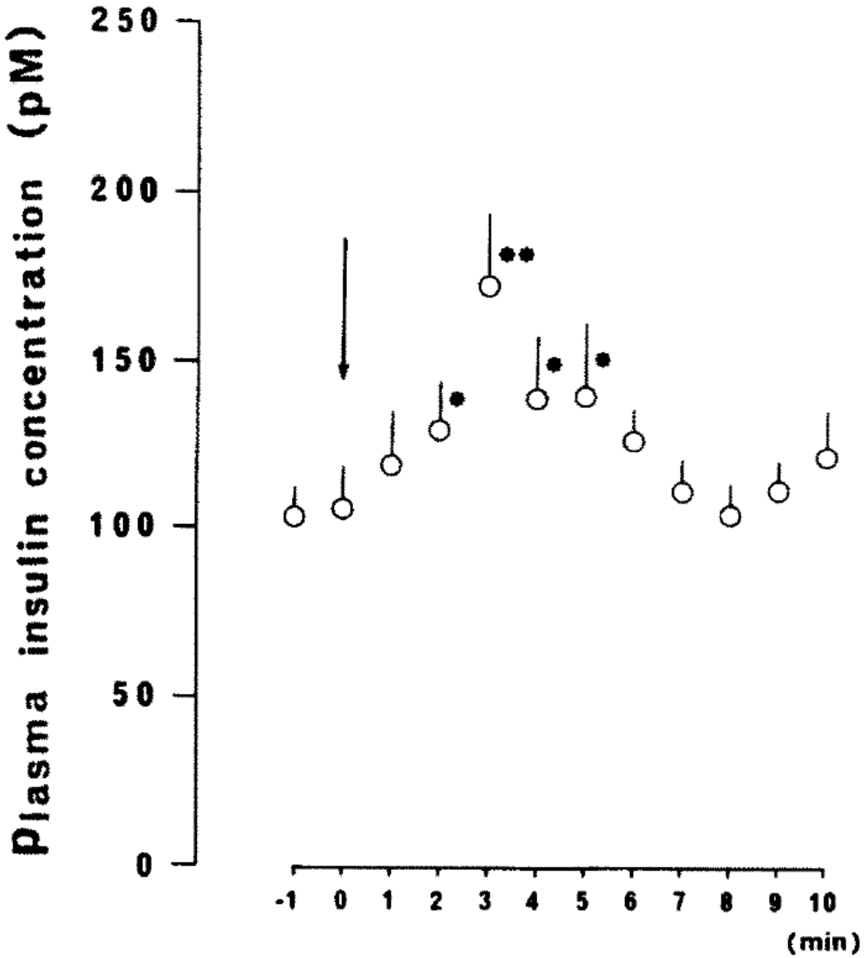


FIG. 1. Changes in the time course of plasma concentrations of insulin after lingual application of 555 mM equilibrated D-glucose (n=9). An arrow indicates the time of application. Values are means±SEM. The insulin concentration reached its peak in 3 min after the application. *$p<0.05$, **$p<0.01$; significantly different from the value at 0 min.

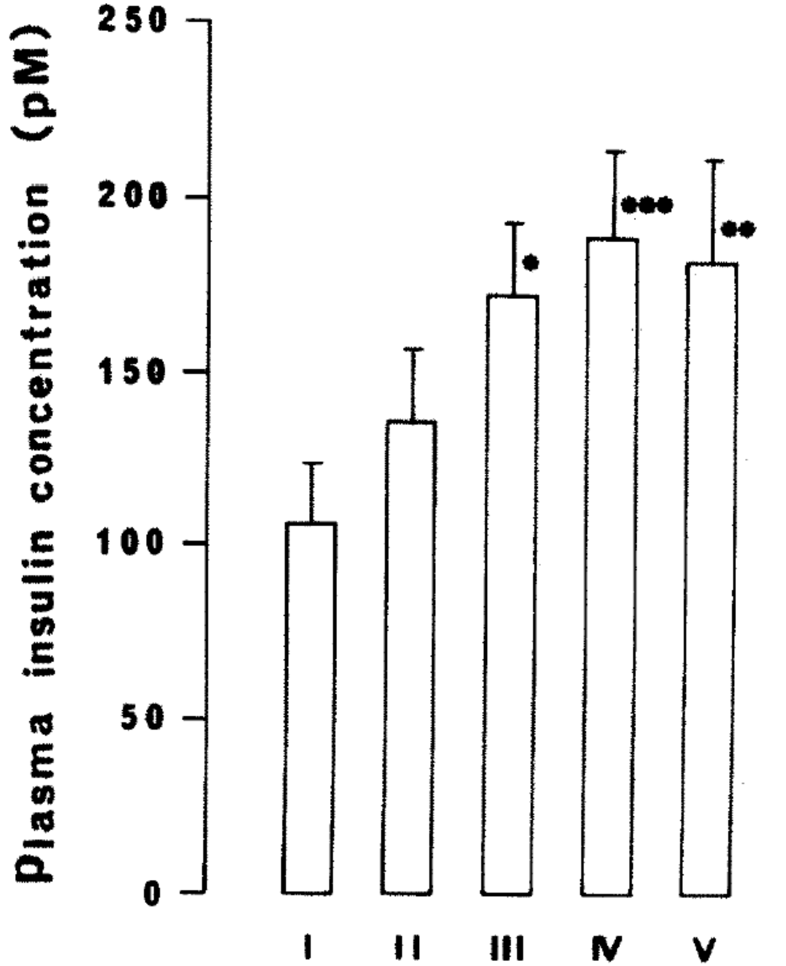


FIG. 2. The effect of equilibrated D-glucose on the release of insulin. Four different concentrations of the glucose (II: 277 mM, n=8; III: 555 mM, n=9; IV: 1110 mM, n=12; V: 2220 mM, n=9) were applied on the tongue as sweet stimuli. Plasma concentrations of insulin 3 min after the stimulation were indicated. Values are means±SEM. *$p<0.01$, **$p<0.005$ and ***$p<0.001$; significantly different from the value without stimulation (I: n=8).

Yamazaki, M., et al. Brain Res. Bulletin 17:271, 1986.

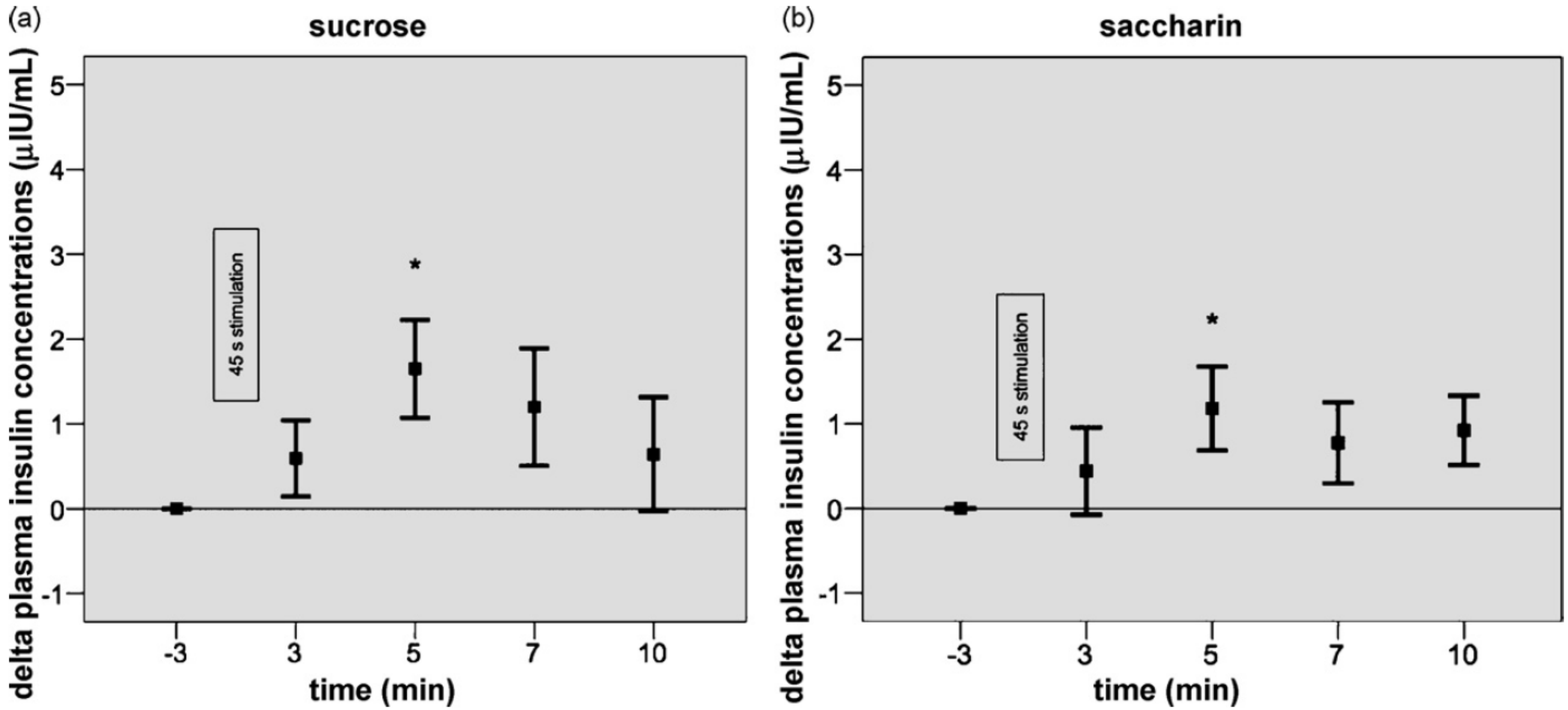
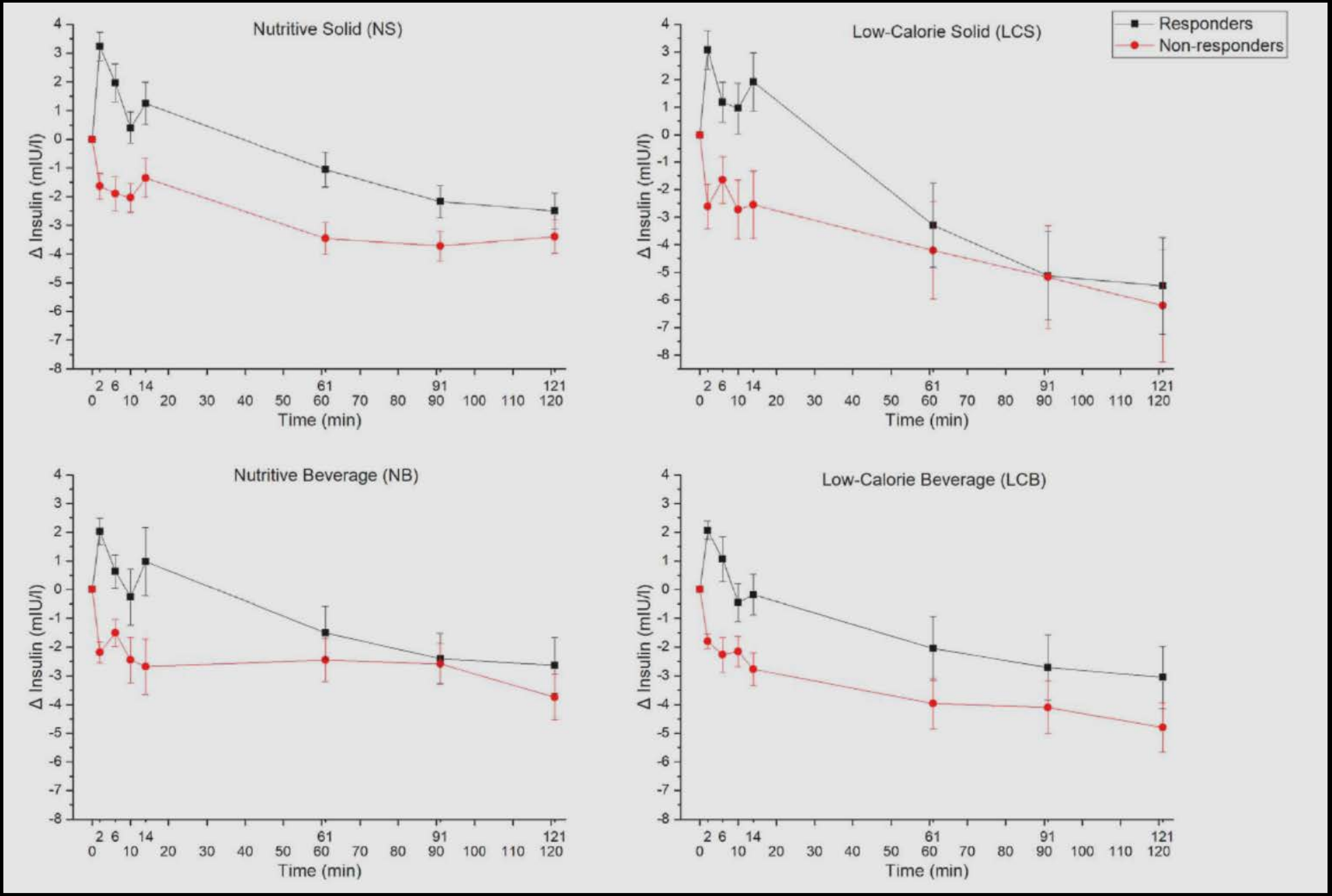


Fig. 2. (a) Effect of taste stimulation with sucrose on plasma insulin concentrations from baseline (µIU/mL) of healthy humans ($n = 20$) (means, S.E.M.) after subjects sipped and spat out the solutions after 45 s. An arrow indicates $t = 0$ min. Significant differences (*) were found between concentration before stimulation and 5 min after sucrose stimulation ($p < 0.05$). (b) Effect of taste stimulation with saccharin on plasma insulin concentrations from baseline (µIU/mL) of healthy humans ($n = 20$) (means, S.E.M.) after subjects sipped and spat out the solutions after 45 s. An arrow indicates $t = 0$ min. Significant differences (*) were found between concentration before stimulation and 5 min after sucrose stimulation ($p < 0.05$).



Dhillon et al., Physiol & Behav 2017;181:100-109

LCS	Stimulation	N	outcome	Sampling
Saccharin	Swish	5	↑ Significant	
Saccharin	Drank	9	↓Glu	no Insulin
Saccharin	Drank	4	Not Significant	
Saccharin	Drank	14	Not Significant	1 blood @ 5 mins.
Saccharin	Swish	15	Not Significant	
Saccharin	Swish	17	Not Significant	
Aspartame	Drank	14	Not Significant	1 blood @ 5 mins.
Aspartame	Swish	15	Not Significant	1 blood @ 5 mins.
Aspartame	Swish	15	Not Significant	
Aspartame	Tablet	12	Not Significant	
Ace-K	Drank	14	Not Significant	1 blood @ 5 mins.
Cyclamate	Drank	14	Not Significant	1 blood @ 5 mins.
Sucralose	Drank/MSF	8	Not Significant	1 Blood @ 15 Mins.
Sucralose	Swish	64	↑Unreliable	

LCS	Stimulation	N	outcome	Sampling
Saccharin	Swish	5	↑ Significant	
Saccharin	Drank	9	↓Glu	no Insulin
Saccharin	Drank	4	Not Significant	
Saccharin	Drank	14	Not Significant	1 blood @ 5 mins.
Saccharin	Swish	15	Not Significant	
Saccharin	Swish	17	Not Significant	
Aspartame	Drank	14	Not Significant	1 blood @ 5 mins.
Aspartame	Swish	15	Not Significant	1 blood @ 5 mins.
Aspartame	Swish	15	Not Significant	
Aspartame	Tablet	12	Not Significant	
Ace-K	Drank	14	Not Significant	1 blood @ 5 mins.
Cyclamate	Drank	14	Not Significant	1 blood @ 5 mins.
Sucralose	Drank/MSF	8	Not Significant	1 Blood @ 15 Mins.
Sucralose	Swish	64	↑Unreliable	

Extinction

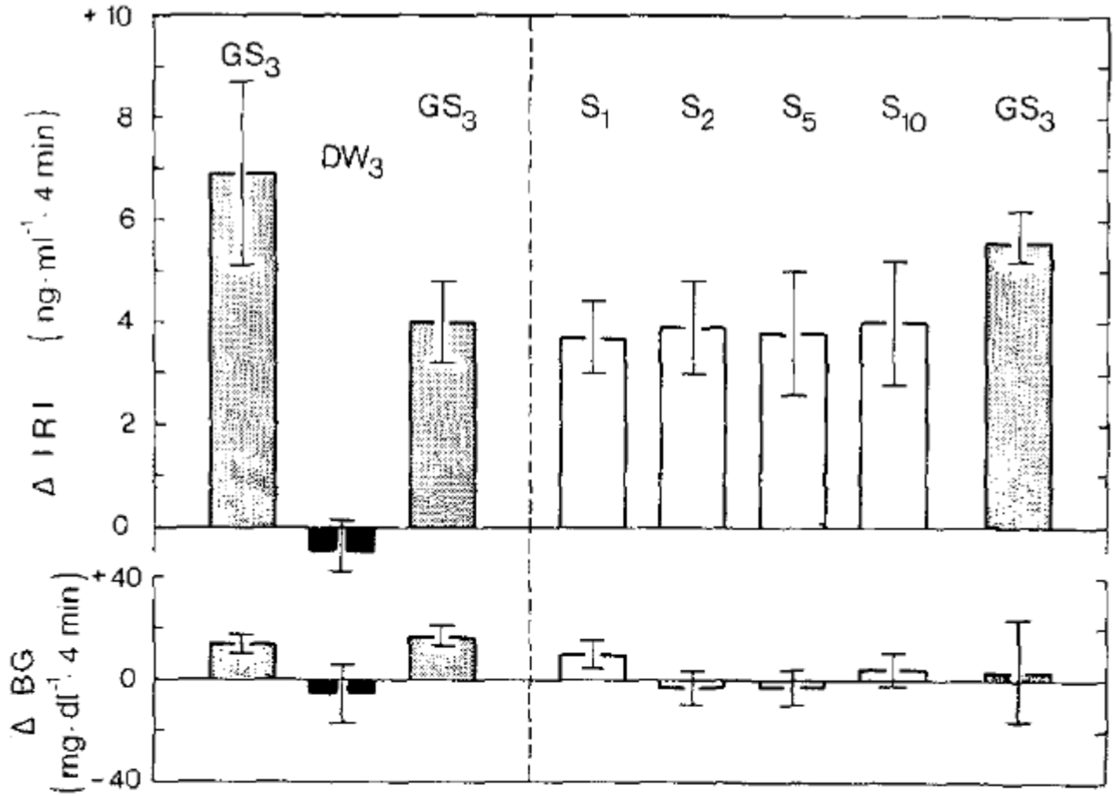
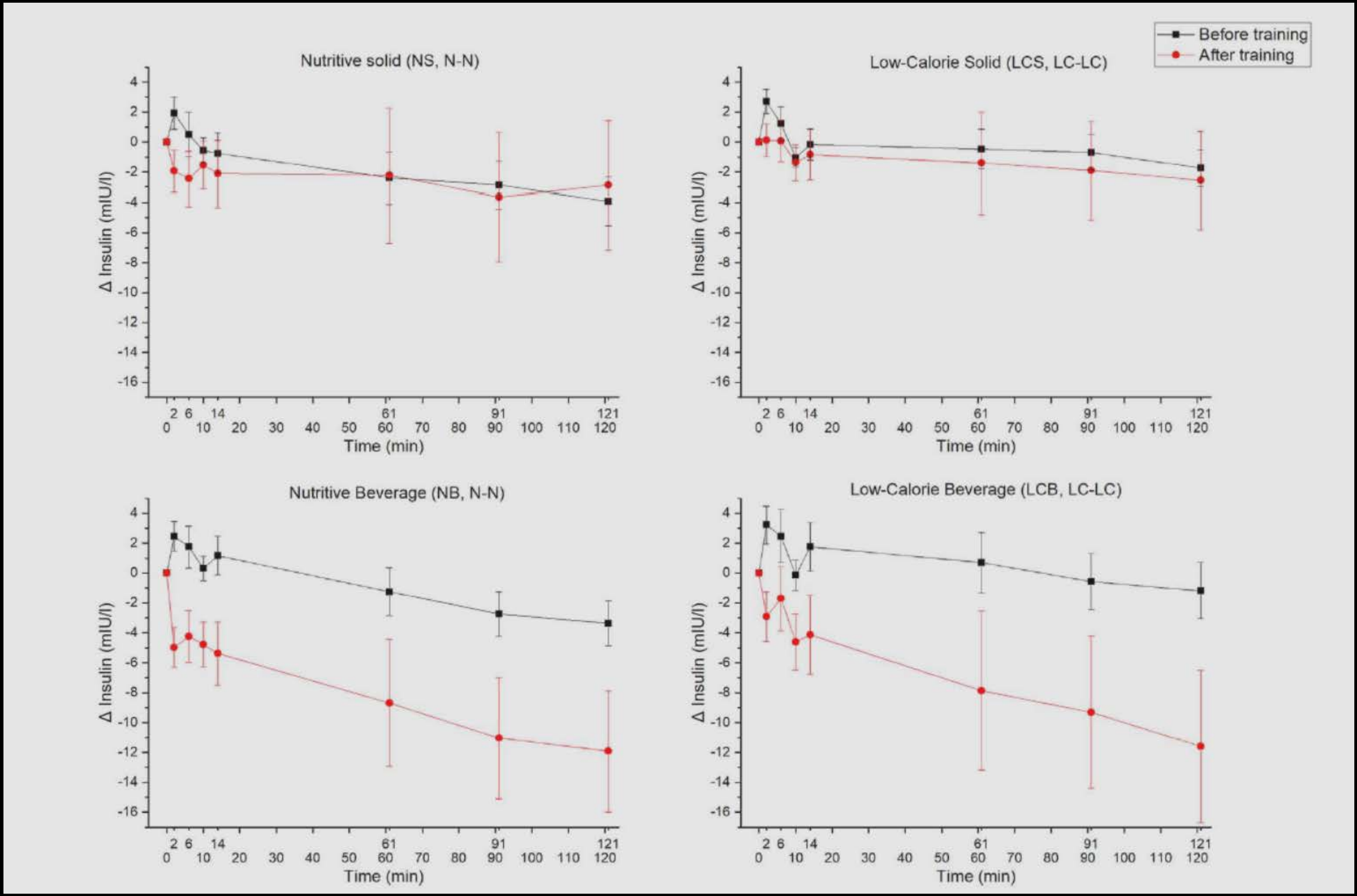


Fig. 3. Cephalic phase insulin response-amplitudes and corresponding glucose changes following different oral stimuli of 3 rats (Mean ± SEM). In the initial phase of the experiment response-amplitudes were twice measured following the third consequetive presentation of glucose + saccharin, GS_3 or distilled water, DW_3. S_1–S_{10} represent the attempted extinction phase of the experiment. S_1 and S_2 as well as S_5 and S_6 were separated by one day of normal feeding, the other extinction trials were performed with intervals of one hour on the same day. At the end of the experiment glucose + saccharin was given again as a control

Berthoud et al., Diabetologia 1981;20:393-401



Dhillon et al., Physiol & Behav 2017;181:100-109

LCS-CPIR SCENARIOS

- Promotes CPIR in the absence of carbohydrate energy
  - Reduction of glycemia leading to hunger and increased energy intake

- Extinguishes CPIR
  - Loss of regulatory signal leading to increased energy intake

Fundamental Questions about the CPIR

- Stimulus property
  - Sweetness
  - Chemical Specificity (LCS; glucose anomers) (Yamazaki & Sakaguchi Br Res Bull 1986;17:271-274)
- Transduction mechanism
  - T1R2-T1R3 receptor
  - ATP-gated K^+ sensor (Glendinning et al AJP 2015;309:R552-R560)
- Route of action
  - Primary
  - Secondary (TRC GLP-1) (Kokrashvili et al BJN 2014;111:S23-S29)

Initial Outstanding Questions

- Functional:
  - Are CPR reliable?
  - Are there responders and non-responders?
  - To what extent do CPR impact nutritional status (appetite, food choice, digestion, absorption, metabolism)?
  - Do CPR contribute to health disorders?
  - Can CPR be used for preventive or therapeutic purposes?
- Mechanistic:
  - Identification of effective stimuli properties
  - Identification of receptors
  - Determine primary and secondary impacts
  - Establish best practices assessment methods