affinity binding site (site 1) shown in Fig. 1A. With higher concentrations of (+)-[^{3}H]amphetamine (>200 nM), as well as unlabeled (±)-amphetamine sulfate (100 μM) for measuring nonspecific binding, the presence of a lower affinity binding site (site 2) became apparent. In addition, comparatively large differences in structure-activity relationships were observed for a series of amphetamine derivatives in displacement studies of the lower affinity site (Fig. 1C). Whether this represents a difference in the pharmacologic profile between sites 1 and 2, or simply the fact that the binding to site 1 represented only 20 to 30 percent of the total binding, making resolution of structure-activity differences for this site more difficult, is not yet clear. Nevertheless, the brain levels of amphetamine following pharmacologically active doses are in the range 2 to 50 μM (J. Axelrod, *J. Pharmacol. Exp. Ther.* **110**, 315 (1954) and thus correspond closely to the apparent affinity constant of (+)-[^{3}H]amphetamine for site 2.

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Sugar Infusion Can Enhance Feeding

Abstract. *An investigation was made of the role of glucose in the regulation of hunger and satiety in the rabbit. Glucose, when infused intraduodenally at a low rate (1 milliliter per minute), produced a decrease in food intake. However, when glucose was infused into the duodenum at a high rate (3 milliliters per minute), the rabbits nearly doubled their food intake during the first half-hour after infusion. It is hypothesized that the rapid arrival of glucose in the duodenum may produce hunger.*

Thirty years ago, Mayer (*1*) postulated the glucostatic theory of hunger, which states that low cellular utilization of glucose stimulates hunger and food intake and that satiety signals terminate food intake when cellular glucose utilization is high. The theory has generated extensive research showing that the administration of glucose suppresses subsequent food intake (*2*). However, the role of glucose in the regulation of hunger and satiety is not that simple. Contrary to what might be predicted on the basis of Mayer's hypothesis, clinicians have often reported that the carbohydrate content of the diet is directly related to hunger (*3*). Similarly, several animal studies have shown that access to a sugar solution can produce an increase in food intake (*3*). These results suggest that, rather than producing satiety, carbohydrates sometimes stimulate appetite and hunger. We now report that when glucose is infused into the duodenum at a slow rate, food intake is suppressed, but that when glucose is infused at a more rapid rate, food intake increases sharply.

Female New Zealand rabbits (2.3 to 3.2 kg) were housed individually in canine flight kennels in a temperature-controlled room (17° to 20°C) with a 12-hour light-dark cycle. Purina Pelleted Rabbit Chow (40 percent carbohydrate, 16 percent protein, and 2 percent fat) and tap water were provided to each animal without restriction throughout the experiments. All the animals were implanted with intraduodenal cannulas (*4*), allowed to reestablish preoperative food and water intake levels, and then adapted to the test apparatus.

Tests were conducted 1.5 hours after lights out. The animals were infused intraduodenally (10 ml per 3 kg) with a 0.3M glucose solution and a 0.15M NaCl solution (equiosmolar control) in randomized order, with an interval of 2 to 3 days between tests (*5, 6*). Infusants were heated to 39°C, the average body temperature of the rabbit. Ten rabbits received infusions at a high rate (3 ml/min) and seven rabbits received infusions at a low rate (1 ml/min). Following the infusion procedure, each cage was equipped with a metal food box that provided input signals to a microprocessor-based data acquisition system (*7*). Food intake was monitored continuously for a 4-hour period, during which the animals were left undisturbed.

When glucose was infused at the high rate, subsequent food intake was en-

Table 1. Meal-related parameters and total food intake as a function of rate of intraduodenal delivery of glucose and saline. Values are means ± standard errors for the first half-hour after infusion.

Rate of infusion	Size of first meal (g)	Meal size (g)	Feeding rate (g/min)	Total food intake (g)
High (3 ml/min)				
Glucose	8.39 ± 0.76*	7.60 ± 0.47†	1.33 ± 0.10‡	11.81 ± 1.39‡
Saline	6.22 ± 0.59	5.15 ± 0.82	0.91 ± 0.14	6.55 ± 1.02
Low (1 ml/min)				
Glucose	5.00 ± 0.44§	4.78 ± 0.95	0.86 ± 0.18	6.69 ± 1.92
Saline	7.67 ± 1.36	6.34 ± 1.70	0.84 ± 0.16	6.34 ± 1.70

*Significantly different from corresponding control value ($P < .02$) (*8*). †$P < .03$. ‡$P < .01$. §$P < .04$.

Table 2. Meal-related parameters and total food intake as a function of volume of intraduodenal delivery of glucose and saline. In the statistical analysis, the volume factor did not enter into a significant interaction. Therefore, all differences were significant regardless of volume. As in the first experiment, during the 4-hour period there was no compensation for the increase in food intake observed in the first half-hour after infusion ($P < .05$). Values are means ± standard errors.

Volume of infusant	First meal after infusion			First half-hour after infusion			
	Latency (minutes)	Meal size (g)	Satiety ratio*	Meal size (g)	Feeding rate (g/min)	Meal frequency	Total food intake (g)
10 ml per 3 kg							
Glucose	3.37 ± 1.26†	7.81 ± 1.18‡	2.87 ± 0.73§	6.82 ± 0.92 ‖	1.27 ± 0.08¶	1.67 ± 0.21**	10.80 ± 1.62††
Saline	6.55 ± 2.36	6.05 ± 1.08	5.78 ± 2.07	5.95 ± 1.09	0.79 ± 0.12	1.17 ± 0.17	6.77 ± 1.23
20 ml per 3 kg							
Glucose	4.17 ± 1.85†	6.98 ± 1.67‡	3.37 ± 0.66§	7.00 ± 1.34 ‖	1.21 ± 0.11¶	1.67 ± 0.21**	10.53 ± 1.11††
Saline	5.84 ± 1.15	4.48 ± 0.92	4.92 ± 0.77	5.05 ± 0.67	1.04 ± 0.10	1.33 ± 0.21	6.25 ± 0.72
30 ml per 3 kg							
Glucose	4.41 ± 1.45†	8.23 ± 1.55‡	3.04 ± 1.02§	7.65 ± 1.50 ‖	1.21 ± 0.07¶	1.67 ± 0.33**	11.20 ± 2.23††
Saline	15.76 ± 4.17	5.77 ± 1.01	3.54 ± 0.31	5.43 ± 1.09	1.15 ± 0.12	1.33 ± 0.21	6.35 ± 0.87

*The ratio of the interval between the first meal after infusion and the next meal to the size of the first meal. †Significantly different from corresponding control value ($P < .02$). ‡$P < .007$. §$P < .03$. ‖ $P < .05$. ¶$P < .02$. **$P < .005$. ††$P < .006$.

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hanced (Table 1) (*8*). The size of the first meal after infusion was significantly greater in the glucose condition than in the saline condition. Also, during the first half-hour after glucose infusion, the mean meal size, mean feeding rate per meal, and total food intake were significantly greater than the same measures taken after saline infusion. The animals ingested approximately 5 g more during the first half-hour after infusion of glucose than they ingested in the saline condition; that is, they nearly doubled their food intake in response to the fast infusion of glucose. Cumulative food intake over the 4-hour measurement period remained approximately 5 g higher in the glucose condition ($P < .01$), so there was no compensation for the increase in food intake in the first half-hour.

Slow infusion of glucose resulted in a significantly smaller first meal than did slow infusion of saline (Table 1). The between-condition difference in mean meal size during the first half-hour was not significant. However, when measured throughout the first hour, mean meal size after glucose infusion (6.15 g) was substantially less than that after saline infusion (8.29 g), a difference approaching significance ($P < .06$).

It was previously shown in our laboratory that intraduodenal infusion of 10 ml of glucose (1 ml/min) suppressed food intake but that increasing the volume to 30 ml enhanced food intake (*9*). We therefore investigated the effect of volume of infusant (delivered at the rate of 3 ml/min) on subsequent food intake. Animal maintenance and surgical procedures were similar to those used in the first experiment. Infusion and testing conditions were also similar, except that six rabbits (2.5 to 3.5 kg) were intraduodenally infused with 10, 20, and 30 ml of 0.3*M* glucose and 0.15*M* NaCl per 3 kg at the rate of 3 ml/min. The results were similar to those of the first experiment (Table 2). Thus, once the infusion rate has been increased sufficiently to produce enhancement of food intake, further increases in volume have no discernible effects (*10*).

These results lead us to hypothesize that glucose produces hunger when it arrives in the duodenum quickly and is absorbed at a rapid rate. This hypothesis has important clinical implications for the control of hunger. Presumably, one could eliminate the hunger-stimulating effect of glucose by slowing the rate at which the food arrives in the duodenum and is absorbed. Ingestion of a diet high in fiber might be one means of avoiding glucose-induced hunger. Fiber increases gastric viscosity, delaying gastric emptying into the duodenum; and, with long-term ingestion of such a diet, the intestinal absorption of glucose is reduced (*11*). Another dietary manipulation that might prevent the hunger-stimulating effects of glucose is to increase the size of the carbohydrate molecules in the diet. Simple sugars are digested and absorbed far more rapidly than are starches (*12*), and animals maintained on a high-sucrose diet ingest more calories than those maintained on a high-starch diet (*13*). Humans historically have ingested starch as their principal carbohydrate; sucrose has only recently been introduced into our diets. Perhaps we have hunger and satiety mechanisms designed to respond to glucose that has been obtained primarily from starches, not simple sugars.

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3. See P. J. Geiselman and D. Novin [*Appetite*, in press] for a review of the seemingly paradoxical conditions under which sugar stimulates appetite and hunger.
4. Intraduodenal cannulas were implanted under sodium pentobarbital anesthesia (Nembutal; 30 mg/kg, intravenously). A small incision was made in the stomach wall near the pyloric sphincter and a cannula (Dow Corning Silastic medical-grade tubing) with inner and outer diameters of 1.02 and 2.16 mm, respectively, was inserted into the proximal duodenum. The cannula was then threaded subcutaneously to the animal's head, where it was attached to a blunted 18-gauge needle and mounted to the cranium with stainless steel screws and dental acrylic. After surgery, the wounds were medicated with topical applications of bacitracin-polymyxin-neomycin (Mycitracin) and the rabbits were injected intramuscularly with kanamycin sulfate (Kantrex).
5. All the animals were also subjected to a mock condition to ensure that the saline infusions neither enhanced not suppressed subsequent food intake. In the mock condition animals were not infused. The test apparatus was attached to the front of the cage and food intake was monitored continuously for 4 hours. Throughout the test period there were no differences in food intake following the mock procedure, saline infusion at the high rate, and saline infusion at the low rate.
6. We could not determine the size of the last meal preceding infusion or the interval between that meal and the first meal after infusion. However, differences in these factors could not have contributed to our results since the variables would have occurred randomly across animals and infusion conditions.
7. See P. J. Geiselman, G. H. Rogers, J. P. Jaster, J. R. Martin, and D. Novin [*Physiol. Behav.* **22**, 397 (1979)] for a detailed description of the data acquisition system used.
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Pavlovian Conditional Tolerance to Haloperidol Catalepsy: Evidence of Dynamic Adaptation in the Dopaminergic System

Abstract. *An experiment with rats has demonstrated that Pavlovian conditioning factors determine the occurrence of tolerance to haloperidol catalepsy. Rats exhibited tolerance only in the environment previously associated with the drug. Previous research involving receptor binding techniques implicated an increase in the number of brain dopamine receptors as the mediator of neuroleptic tolerance. The present findings demonstrate that this change, by itself, cannot account for the conditional occurrence of such tolerance.*

Haloperidol is one of a number of neuroleptic drugs that are effective in treating paranoid schizophrenia. There is direct evidence that haloperidol and most other neuroleptics block dopamine receptors in the brain (*1, 2*). A frequent adverse effect of long-term neuroleptic therapy is tardive dyskinesia, a syndrome of involuntary motor movements commonly involving the buccolingual-masticatory triad (*3–5*). The syndrome is transiently increased on neuroleptic withdrawal, while reintroduction of the drug or an increase in dose can eliminate the signs. Hence it appears that long-term blockade of brain dopamine receptors by neuroleptics eventuates in neuroleptic tolerance, which in turn may contribute to tardive dyskinesia (*2, 3*).

In rats haloperidol produces a charac-

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