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.

PAULA J. GEISELMAN
DONALD NOVIN
Department of Psychology, University of California, Los Angeles 90024

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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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Table 1. Cataleptic response of each group to haloperidol (1.5 mg/kg) at each assessment interval. Values are means ± standard errors.

Minutes after haloperidol injection	Duration of cataleptic response (seconds)		
	Control rats	Rats tested in drug-associated environment	Rats tested in saline-associated environment
25	109.8 ± 16.8	22.8 ± 5.4	108.7 ± 16.5
50	136.8 ± 13.5	45.8 ± 11.3	125.8 ± 13.6
75	169.6 ± 5.7	68.3 ± 15.8	157.6 ± 10.9

teristic neuroleptic syndrome consisting of suppression of spontaneous movements and catalepsy. With repeated administration of the drug, tolerance develops to these effects (*6, 7*). Termination of long-term neuroleptic treatment results in supersensitivity to dopaminergic drugs, such as apomorphine (*8, 9*). Receptor binding studies have shown that repeated neuroleptic administration increases the number of postsynaptic dopamine receptors in the brain, and it has been suggested that such changes underlie both tolerance and supersensitivity to dopaminergic drugs (*2, 10*).

In a series of studies on tolerance to morphine analgesia, Siegel (*11*) proposed that tolerance is the sum of the unconditioned pharmacological effects of a drug and a compensatory conditioned reaction to those effects. According to this proposal, the manifestation of tolerance is determined by the presence of contextual cues coincident with previous administrations of the drug. There is now considerable evidence in support of the theory as it applies to the analgesic effect of morphine (*11, 12*) and the hypothermic effect of ethanol (*13, 14*). We report here that the manifestation of tolerance to the cataleptic effect of haloperidol is governed by Pavlovian conditioning factors.

Two experimental groups, each consisting of 12 male Sprague-Dawley rats (250 to 280 g), received repeated intraperitoneal injections of haloperidol and saline. The two groups differed only in terms of the environment in which haloperidol and saline were consistently administered. One injection environment was a dark room with constant 75-dB background noise. The rat was placed in a clear Plexiglas observation box (27 by 27 by 39 cm) with a black floor. The other injection environment was a brightly illuminated, quiet room where the rat was placed in an observation box with a black and white striped floor. One group of rats received haloperidol injections in the dark, noisy, black-floored environment and saline injections in the bright, quiet, striped environment and the second group received the reverse.

During the tolerance development phase each rat was given 28 injections of haloperidol (3 mg/kg) (in the form of Haldol, 5 mg/ml) and 56 injections of saline. The two substances were injected on different days in accordance with a random sequence in which haloperidol was injected once and saline twice during 3-day periods. For each treatment the rat was transported from the colony to its designated environment and injected with the scheduled substance. The rat then remained in that environment for 150 minutes.

After the tolerance development phase all the rats were tested for the cataleptic effects of haloperidol. Half of the rats in each group were tested in the environment in which haloperidol had been administered. The remaining animals in the two groups were then tested in the environment associated only with saline injections. A third group of 12 rats received only saline injections in both environments during the tolerance development phase. This control group was also tested for haloperidol-induced catalepsy. Six control rats were tested in one environment and six were tested in the other.

Tolerance to haloperidol-induced catalepsy was tested with the standard bar-hanging procedure (*6*). Catalepsy is indexed by the amount of time the animal remains hanging with both paws on the bar. Each rat was given three successive 1-minute tests 25, 50, and 75 minutes after the injection of haloperidol (1.5 mg/kg); thus the maximum catalepsy score was 180 seconds at each assessment interval. The lower dose was used to increase the sensitivity of the test.

Table 1 shows the mean haloperidol catalepsy scores for the different groups at each assessment interval. Within each group there was no difference in performance between the two injection environments, hence the data for the two environments were combined for each group. An overall analysis of variance revealed a significant difference in performance among groups [$F(2, 33) = 12.04$, $P < .001$]. Subsequent pairwise comparisons were computed with Tukey's test.

Ezrin-Waters *et al.* (*15*) obtained catalepsy scores of virtually zero for nondrugged rats on the standard bar-hanging test. Thus, the test dose of haloperidol produced marked catalepsy in our control animals (Table 1). Drug-experienced rats tested in the drug-associated environment showed substantial tolerance to haloperidol catalepsy at each assessment period. Pairwise comparisons revealed that these rats were significantly less cataleptic than the control animals at each assessment interval ($P < .01$). More important, animals tested in the saline-associated environment were significantly more cataleptic at each assessment interval than rats tested in the drug-associated environment ($P < .01$). The amount of catalepsy shown by the former did not differ significantly from that shown by the control animals.

These results demonstrate tolerance in haloperidol-experienced animals following an expected drug administration but not following an unexpected one. An increase in the number of dopaminergic receptors resulting from long-term neuroleptic exposure (*2, 10*) cannot account for such tolerance. Rather, it appears that cues previously associated with neuroleptic administration are critical for engaging mechanisms that counteract the cataleptic effect of haloperidol in producing tolerance.

CONSTANTINE X. POULOS
Addiction Research Foundation, Toronto, Ontario, Canada M5S 2S1
RILEY HINSON
Department of Psychology, University of Western Ontario, London, Ontario, Canada N6A 5C2

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