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Pimozide Blocks Reinforcement but not Priming from MFB Stimulation in the Rat

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WASSERMAN, E. M., Y. GOMITA AND C. R. GALLISTEL. *Pimozide blocks reinforcement but not priming from MFB stimulation in the rat.* PHARMAC. BIOCHEM. BEHAV. 17(4) 783–787, 1982.—When given non-contingent pretrial stimulation (priming stimulation) rats ran an alley for brain-stimulation reward faster than when there was no priming. This is one manifestation of the priming effect of rewarding stimulation. After treatment with the neuroleptic, pimozide, the first few trials fell in the range of normal primed performance when the rats were primed, and in the range of normal unprimed performance when they were not. In either case, an extinction-like decline in performance occurred after the first few trials. Run in a T-maze with water in one arm and a lever producing brain stimulation reward in the other, thirsty rats chose the stimulation reward when primed and the water reward when unprimed. Pimozide in doses that produced extinction of Skinner box responding did not alter this effect of priming on reward preference. These results demonstrate that the priming effect is unaltered by doses of pimozide that block the reinforcing effect of the stimulation.

Pimozide Priming Reinforcement Brain-stimulation reward

REWARDING electrical stimulation of the medial forebrain bundle (MFB) has a transient aftereffect that motivates or "primes" the animal. Administering brain stimulation to a rat before it runs an alley for identical stimulation increases its running speed [3]. Priming also increases the probability that thirsty rats will choose brain stimulation over water in a T maze [1]. The difference between primed and unprimed performance in a runway is reliable [6], and it is as prominent on the first trials of a session as on later trials [5]. If pimozide blocked the priming effect of rewarding stimulation, the performance of primed rats treated with pimozide ought to be slower on the first few trials of the session than the performance of primed rats undergoing normal extinction. However, the previous paper reported no significant difference between these two conditions on any of the first 10 trials (8 rats, each serving in both conditions; see Fig. 5 in [4]). The fact that extinction-producing doses of pimozide had no effect on the initial performance of primed rats suggests that the drug does not block the priming effect of the stimulation, only its reinforcing effect [2]. This would imply that the two effects are mediated by neurochemically distinct substrates, and that the priming effect is not a secondary consequence of the reinforcing effect.

The experiments reported in the preceding paper [4] (see also [2]) did not, however, verify the presence of a priming effect and demonstrate that it remained unaltered by pimozide. We now report the verification of a priming effect in six rats and the demonstration that extinction-producing doses of pimozide left the effect intact in all six. In four of the rats, the priming effect was demonstrated by non-overlapping populations of primed and unprimed running speeds. In the remaining two, it was demonstrated in a T-maze where thirsty rats chose between water and brain stimulation reward (BSR).

METHOD

Experiment 1

The subjects were four male Sprague-Dawley rats with monopolar electrodes in the posterior lateral hypothalamus. They were used in the preceding study [4], which see for details of implantation, training, etc. They were tested in the 1.8 m runway described in the preceding paper. Upon reaching the goal end and pressing the lever, they received one 0.5 sec train of stimulation composed of 0.1 msec cathodal pulses at 100 pps. The current was set at 400–600 μA to produce a maximal priming effect (a maximal difference between the running speeds on primed versus unprimed trials). In sessions with primed trials, the rat was removed from the runway as soon as it received its reward and placed in a 20 cm square box that stood beside the runway, where 25 seconds later it received 10 trains of priming stimulation, identical to the trains received as a reward, delivered at the rate of

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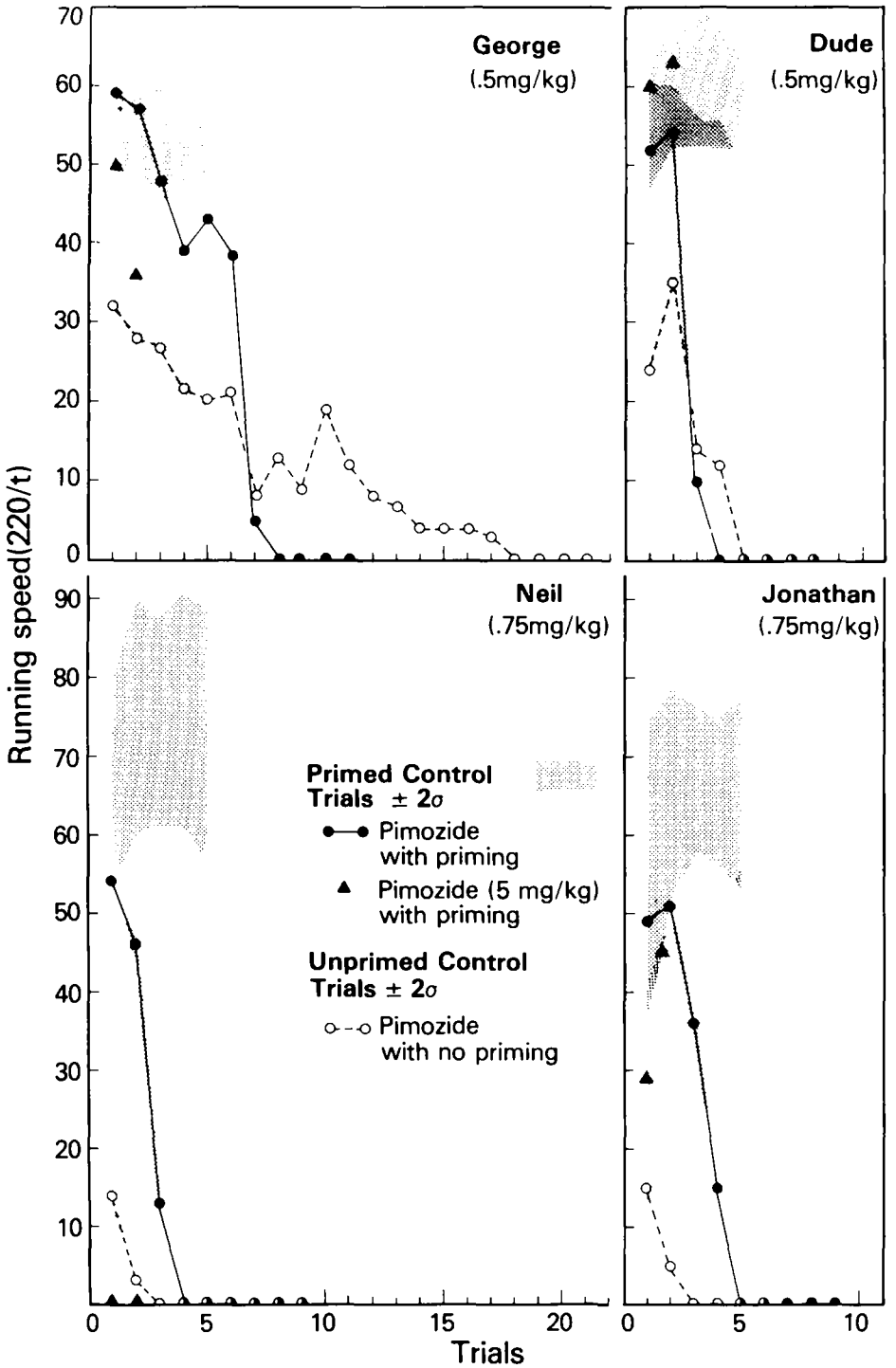

FIG. 1. Trial-by-trial running speeds under pimozide, with and without pretrial priming. The shaded areas indicate the range (mean±2 standard deviations) of performance under control (no drug) conditions. Only the first two trials are plotted from the high dose (5 mg/kg) session (triangles).

1 train per second. When priming ceased, the rat was transferred from the priming box to the startbox of the runway. Five seconds after the cessation of priming, the door to the startbox opened. The running speed from the opening of the door to the press on the goal lever was recorded on chart paper at 220/t, where t=latency in seconds. In sessions with unprimed trials, the stimulator that delivered the priming stimulation was disconnected.

Each rat was run in 8 primed sessions and 5–8 unprimed sessions, with 15–30 trials per session. From these data we

TABLE 1

PRIMED AND UNPRIMED FIRST TRIAL RUNNING SPEEDS WITH AND WITHOUT PIMOZIDE

	Control (No Pimozide)		Pimozide		
Rat	Primed Mean (n, σ)	Unprimed Mean (n, σ)	Primed Mean (n, σ)	Unprimed Mean (n, σ)	5 mg/kg Primed
George	53 (8, 4.5)	27 (8, 7.0)	54 (2, 7.1)†	24 (2, 11.3)§	50†
Dude	54 (8, 3.7)	28 (5, 16.0)	54 (2, 3.6)†	28 (2, 6.4)§	60†
Neil	67 (8, 6.4)	22 (8, 9.0)	54 (1, —)†	14 (1, —)§	0§
Jonathan	56 (8, 9.3)	25 (8, 6.9)	49 (1, —)*	15 (1, —)§	29‡ 45*¶

Greater than unprimed mean (*=$p<0.05$, †=$p<0.01$, 1-tailed).
Less than primed mean (‡=$p<0.05$, §=$p<0.01$, 1-tailed).
¶2nd trial of the 5 mg/kg session.

computed the mean and standard deviation of the running speeds under both primed and unprimed conditions for each of the first five trials. The shaded areas in Fig. 1 show the regions lying within ±2 standard deviations of the means.

The rats were then tested at least once in each of three drug conditions. Drug testing sessions, which were separated from each other by at least 2 days, were run 4 hours after the IP injection of a dose of pimozide dissolved in a 3% tartaric acid vehicle. The conditions were: 0.5–0.75 mg/kg pimozide with priming; 0.5–0.75 mg/kg pimozide without priming; 5.0 mg/kg pimozide with priming.

Experiment 2

The rats were run in a T maze similar to that used in [1]. At the end of the right arm was the nozzle of a water bottle. A lever that delivered brain stimulation reward (BSR) was mounted at the end of the left arm. Two additional rats similar in all respects to those in Experiment 1 were trained under 20-hour water deprivation to run to the right for 5 sec of drinking. During this period, no BSR was delivered. When the rats were running readily for water, BSR was introduced as a reward for running to the left and pressing the lever. The stimulation was the same as in Experiment 1, with current set individually for each subject at a level that caused the animal to choose stimulation only when primed and otherwise to choose water. Priming consisted of 10 trains of stimulation identical to the reward stimulation, with 0.5 sec between trains. At the end of each trial, the rat was placed in its home cage, which was adjacent to the maze during the training or test session. After 20 sec, either priming was administered or the animal was left in the cage for an additional 10 sec before the start of the next trial.

When the subjects (20-hr deprived) were choosing water on about 90% of unprimed trials and brain stimulation on about 70% of the primed trials, they were run in a series of 5 control sessions. Each session consisted of two blocks of 5 trials each, one block primed and one block unprimed. The number of choices of each goal under each condition was recorded. The order of the primed and unprimed blocks was reversed in alternate sessions. Then, two sessions were run 4 hours after treating each rat with a dose of pimozide that had previously been determined to be sufficient to cause extinction. The order in which the primed and unprimed blocks were run was counterbalanced across the two sessions. Between drug sessions, the rats were run at least once to check for recovery. Immediately following the last drug session, extinction of lever-pressing was tested in a Skinner box.

RESULTS

Experiment 1

After treatment with 0.5–0.75 mg/kg pimozide, all four rats ran much faster on the first few trials when primed than when not primed (Fig. 1). When primed, their initial performance fell within the range of their usual primed performance and clearly faster than their usual unprimed performance. When unprimed, their performance was as slow as their usual unprimed performance. In either case, the rats extinguished in 6–22 trials.

Even after 5.0 mg/kg—a dose 10 times greater than that required to block reinforcement—three of the four rats ran within the range of normal primed performance and above the range of normal unprimed performance on at least one of the first two trials.

Table 1 shows means and standard deviations for first trial performance under control conditions, first trial data for the drug conditions, and significance levels for differences, as computed by t-tests. The t-test is used to assess the probability that the speeds observed under pimozide on a given trial came from the same population as the control sample. It is valid even when only a single observation is made in the test condition ([7], p. 224). In all four rats, the first trial primed running speed under pimozide (0.5–0.75 mg/kg) was significantly faster than unprimed control trials and not significantly different from primed control trials. In all four rats, the first trial unprimed speed under pimozide was significantly slower than the primed control trials and not significantly different from the unprimed control trials.

Experiment 2

The effect of pretrial stimulation was also demonstrated under both control and drug conditions. Table 2 arranges the data in 2×2 contingency tables that exhibit the effect of priming on reward preference in each of the two conditions (control and drugged). In both conditions, Fisher's exact test yields a very low probability that choice was independent of priming. Priming caused the rats to select BSR over water significantly more often in both conditions. Table 3 re-

TABLE 2

EFFECT OF PRIMING ON REWARD CHOICE UNDER CONTROL AND PIMOZIDE CONDITIONS

Rat:	EW-1		EW-2	
	Number of Water Choices	Number of Stimulus Choices	Number of Water Choices	Number of Stimulus Choices
		Control (No Pimozide)		
Primed	6	19	10	15
Unprimed	23	2	20	5
	$p<0.001$		$p=0.004$	
		Pimozide Condition		
Primed	4	6	3	7
Unprimed	10	0	9	1
	$p=0.005$		$p=0.01$	

Probabilities computed by Fisher's exact test of independence, 1-tailed.

TABLE 3

REWARD CHOICE AS A FUNCTION OF PRIMING IN UNDRUGGED AND PIMOZIDE TREATED RATS

Rat:	EW-1		EW-2	
	Number of Water Choices	Number of Stimulus Choices	Number of Water Choices	Number of Stimulus Choices
		Unprimed Condition		
Undrugged	23	2	20	5
Pimozide	10	0	9	1
	$p=0.50$		$p=0.43$	
		Primed Condition		
Undrugged	6	19	10	15
Pimozide	4	6	3	7
	$p=0.28$		$p=0.44$	

Probabilities computed by Fisher's exact test, 1-tailed.

arranges the same data in another set of 2×2 tables to show that the preference for water in the unprimed condition and the preference for BSR in the primed condition were unaffected by pimozide. Fisher's exact test of independence gives no reason to reject the assumption that the preference of a primed rat for BSR is independent of the drug treatment; and likewise for the unprimed rat's preference for water.

When the pimozide treated rats were tested in a Skinner box immediately after the T-maze testing, they exhibited the same sort of extinction portrayed in Fig. 6A of the preceding paper.

DISCUSSION

The results demonstrate that the priming effect of electrical stimulation of the MFB is not sensitive to dopaminergic blockade by pimozide and therefore must have a different neurochemical substrate from that of reinforcement. The stimulation must affect either directly or transynaptically two separate pathways or anatomical loci. One is associated with the perception or memory of the stimulation and is responsible for the reinforcement of lever pressing behavior. When this process at this locus is blocked, e.g., by pimozide, extinction ensues. The other pathway mediates the priming effect, the shortlived motivation-like changes in the animal's performance immediately following stimulation. This latter system is able to function independently of the reinforcement system and may be presumed to have a pharmacology of its own.

The reward and priming pathways may share a common first stage, that is, the fibers directly excited by the electrode current may be the same for both effects. Or, since the MFB is a heterogenous collection of fibers, priming and reward may be mediated by independent pathways that pass in close proximity to the electrode. In either case, the priming effect is not a secondary consequence of the reinforcing effect.

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