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Technique for Assessing the Effects of Drugs on Timing Behavior

Before a drug can safely be recommended for relief of a specific physiological malfunction it must be checked for possible deleterious effects upon other systems. Careful consideration must also be given to the possibility of "toxic" effects upon normal adaptive behavior, particularly in the case of those drugs that are known to produce behavioral changes. In view of the importance of temporal orientation in normal behavioral functions, the effect of drugs upon timing would appear to constitute a primary area of investigation. The purpose of this report is to describe a method, based on earlier work by Skinner (*1*), for producing and measuring timing behavior in experimental animals, and to present some data resulting from the administration of amphetamine and alcohol (*2*).

White rats, deprived of water for 22.5 hours, were placed in a small chamber containing a lever and a mechanism for automatic delivery of a small drop of water. In the first session every depression of the lever by the animal produced the water reinforcement. In all following sessions, each 2 hours long, reinforcement was contingent on lever presses spaced at least 21 seconds apart. That is, a response produced the water only if it followed the preceding lever depression by at least 21 seconds. Programming and recording were accomplished automatically by timers, magnetic counters, and associated relay circuits.

Using this procedure, Wilson and Keller have demonstrated that the rate of lever pressing is inversely related to the length of the required delay between responses (*3*). Since drug-produced general excitatory or depressive effects might themselves alter the rate of lever pressing (*4*), a more useful measurement of the timing is the relative frequency distribution of interresponse times (intervals between successive responses). This distribution, which displays no consistent trend after the animals have been exposed to the experimental procedure for 30 to 60 hours, is illustrated by the "saline" control records of Fig. 1. The large proportion of responses that are spaced less than 3 seconds apart is typical and unexplained, but the remainder of the distribution provides a clear description of the timing behavior. The relative frequencies of interresponse times rise to a peak between 18 and 21 seconds and then display a gradual decline.

The center sections of Fig. 1 illustrate the effects of two relatively large doses of *dl*-amphetamine sulfate administered subcutaneously, 5 minutes prior to the experimental session, in a solution of 1 mg/ml of physiological saline. Increasing doses of this drug tend to move the peak of the distribution progressively toward the short interresponse times. That is, the animals press the lever more frequently before the required interval has elapsed.

In addition to the shifts in the relative frequency distribution, large increases in the total response output occurred (Table 1). In contrast, intraperitoneal injection of 3 ml of a 10-percent ethyl alcohol solution, representing a dose of 1 mg/kg, produced a decline of more than 50 percent in the rate of lever pressing. The relative interresponse time frequencies, however, as shown in the lower section of Fig. 1, displayed little change except for a slight leveling of the total distribution. Although alcohol, in the dose administered, produced a general depression of lever-pressing behavior, there was relatively little effect upon the timing.

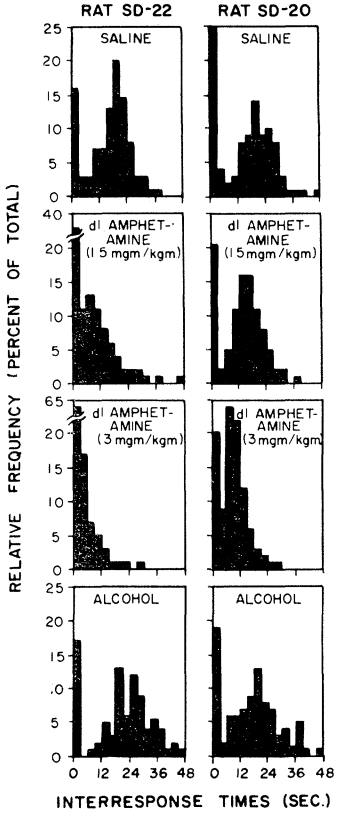

Fig. 1. Relative frequency distributions of the time intervals between successive lever presses. Each distribution represents one animal's performance in a single 2-hour session.

Table 1. Total number of lever presses emitted during each 2-hour session

Rat	Saline	*dl*-Amphetamine		Alcohol
		1.5 mg/kg	3.0 mg/kg	
SD-20	471	534	854	201
SD-22	433	820	1816	176

This technique for generating and measuring timing behavior is applicable to the minimally restrained individual organism, produces stable behavior over long periods of time, has procedural simplicity, and permits automatic programming and recording. The orderly response to drugs, illustrated by this data, indicates the feasibility of including this method in programs designed to screen drugs for their behavioral effects.

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References and Notes

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Altering Juvenility with Auxin

One of the most carefully described instances of the juvenile phase in plant development is that of the Brussels sprouts (*Brassica oleracea gemmifera* L. var. Kolom) (*1, 2*). Plants of this species must reach a certain age—generally 11 weeks—before they are sensitive to the floral inductive experience of low temperature.

The effectiveness of low temperatures on flowering is known for many species of plants (*2–5*). The recent report by Moore (*6*) that auxin applied before low temperature may accentuate the bolting response of cabbage suggests the possibility that auxin levels insufficient for bolting may be a partial basis for juvenility.

This paper (*7*) deals with the influence of auxin on the low temperature induction of floral initiation in Brussels sprouts. It is shown that an application of auxin during the cold treatment has a promotive effect on flowering and can effectively shorten the juvenile phase.