Pargyline-Induced Increases in Sensitivity to the Effects of Drugs on Operant Behavior in Pigeons

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Abstract. Pigeons responded under a multiple fixed-interval 5-min, 30-response fixed-ratio schedule of food reinforcement. Acute pargyline doses between 10.0 and 50.0 mg/kg (i.m.), given immediately prior to the session, decreased responding. Daily administration of 50 mg/kg pargyline (24 mg/kg, every 12 h) initially decreased responding. Tolerance developed so that after 4 days of daily pargyline, responding had returned to control values. Chronic pargyline resulted in an enhanced sensitivity to the effects of d-amphetamine, ephedrine, tyramine, and morphine on schedule-controlled responding. Both d-amphetamine and pentobarbital increased fixed-interval responding at relatively low doses, while higher doses decreased responding. Daily pargyline resulted in an increased sensitivity to both the increases and decreases in response rates produced by d-amphetamine. In contrast, sensitivity to pentobarbital was not changed after daily pargyline. Ephedrine, tyramine, and morphine only decreased fixed-interval responding. Chronic pargyline resulted in an increased sensitivity to the response-rate decreasing effects of ephedrine, tyramine, and morphine. In addition to the increased sensitivity of fixed-interval responding to the effects of tyramine, the dose-effect curve for fixed-ratio responding was also a shifted to the left. Daily pargyline did not result in changes in sensitivity of fixed-ratio responding to the effects of the other drugs tested.

Key words: Operant behavior — Tolerance — Pargyline — Pigeons — Sympathomimetics — Pentobarbital — Morphine.

Indirectly-acting sympathomimetics are thought act by releasing biogenic amines from nerve terminals (Burn and Rand, 1958; Trendelenburg, 1963). In the peripheral nervous system tyramine, d-amphetamine, and other indirectly-acting sympathomimetics produce their effects on heart rate, blood pressure, bronchial smooth muscle tone, etc. by releasing catecholamines stored within adrenergic nerves and related tissues (Potter and Axelrod, 1963; Trendelenburg, 1963; Smith, 1966). In addition to their effects on the peripheral nervous system, amphetamine and other indirectly-acting sympathomimetics produce increases in spontaneous locomotor activity in rodents (Smith, 1963; Van Rossum and Hurkmans, 1964; Costa et al., 1972) and stimulate, suppress, and reinforce operant responding (McMillan, 1968a, b; Pickens and Thompson, 1968; Tilson and Sparber, 1972; Goldberg, 1973). It has been proposed that the stimulation of locomotor activity is at least in part due to the drug-induced release of catecholamines in the brain (Van Rossum and Hurkmans, 1964; Carlsson, 1970). In support of this hypothesis, it has recently been demonstrated that ventricular perfusion of the cat brain with d-amphetamine will cause a release of radiolabeled dopamine into the lateral ventricle (Chiueh and Moore, 1975). In addition, drugs that inhibit the conversion of tyrosine to catecholamines result in a decreased sensitivity to psychomotor stimulants (Weissman et al., 1966; Dominic and Moore, 1969). Inhibition of monoamine oxidase (MAO) with pargyline resulted in increased sensitivity to the locomotor stimulant effects of a series of N-ethyl amphetamines (Tessel et al., 1975), consistent with the hypothesis of a drug-induced intraneuronal release of catecholamines in the brain which produces the locomotor stimulation. Narcotic analgesics also produce dose-related increases in spontaneous locomotor activity; pretreatment with MAO inhibitors resulted in increased
sensitivity and amine depletion resulted in decreased sensitivity to the locomotor stimulant effects of narcotics (Hollinger, 1969; Carrol and Sharp, 1972; Villarreal et al., 1973), suggesting that the effect of narcotics may also be due to the release of catecholamines in the brain central nervous system.

The present study was conducted to determine if the sensitivity of operant responding to the effects of morphine and a series of sympathomimetic amines could be enhanced by daily injections of the MAO inhibitor pargyline. Aprison and Ferster (1961) previously demonstrated an enhanced sensitivity of pigeons to the effects of 5-hydroxytryptophan on operant behavior after MAO inhibition by iproniazid. In the present study, pargyline-induced increases in sensitivity were determined by comparing dose-effect curves before and during daily pargyline. Pentobarbital doses were also tested, since it, like amphetamine, produced increases in food-reinforced responding under a multiple FI-FR schedule (Rutledge and Kelleher, 1965).

METHODS

Subjects. Subjects were six male pigeons (three White Carneaux and three Silver Kings), weighing between 400 and 600 g when allowed free access to food and water. All birds had prior histories of operant responding. None had received any drugs for at least 3 months prior to the start of the study. Birds were deprived of food until they reached 80% of their free feeding weights; they were maintained at this level by post-session supplemental feeding.

Apparatus. The three experimental chambers were closely similar to those described by Ferster and Skinner (1957). White noise was continuously present in each chamber to help mask extraneous noise. Chambers were ventilated by exhaust fans. An acoustic response key (1.9 cm diameter) could be transilluminated by blue or red 7 W light bulbs and was operated by a force equivalent to a weight of about 15.0 g. Four seconds access to mixed grain served as an approximation of the key-peck response. Under the terminal FI time, required for the emission of one-fourth of the total responses.

Procedure. Pigeons were trained to respond by reinforcing successive approximations of the key-peck response. Under the terminal schedule conditions food was presented following the first response after 5 min in the presence of a red light (fixed-interval 5 min; FI 5), or after the thirtieth response in the presence of a blue key light (fixed-ratio 30 response; FR 30). The key lights were extinguished and the food hopper was illuminated by a white light during food presentation. If a bird did not respond within 60 s after each FI 5 had elapsed, no food was delivered and the schedule advanced to the next FR 30 component. Similarly, if 30 responses were not emitted within 60 s in each FR 30 component, no food was delivered and the schedule was switched to the next FI 5 component. Each session consisted of ten FI 5 and ten FR 30 components which alternated throughout the session. Under these schedule conditions, the session length was approximately 60 min. Each bird was run for a minimum of 30 days before drug testing. Sessions were conducted daily. Stability in all cases was defined as no consistent upward or downward trend in response rate or quarter-life (QL) across sessions.

Dose-Effect Curves. Test doses of morphine, pentobarbital, d-amphetamine, tyramine, and pargyline were administered immediately before the start of the session. Drugs were dissolved in saline and injected into the breast muscle of the bird. Drugs were tested no more frequently than every fifth day; saline was injected on intervening days. Doses were tested in an increasing dose sequence.

In the second phase of the experiment, pargyline was administered every 12 h, at a dose of 25 mg/kg. One of the two daily injections was given immediately before the session. After responding had stabilized under the chronic pargyline regimen, morphine, d-amphetamine, tyramine, and pentobarbital dose-effect curves were re-determined. Drugs were tested every fifth day; on test days both pargyline and the test dose were injected before the session.

Data Analysis. Response rates were calculated in responses/s for FI and FR components. QL, a measure of response distribution within FI components, was computed on the basis of average response rates and successive 30-s segments of each FI component according to the method of Collub (1964). This statistic represents the average amount of time, expressed as a percentage of the total FI time, required for the emission of one-fourth of the total responses in each FI.

Drugs. Morphine sulfate, d-amphetamine sulfate, ephedrine sulfate, tyramine hydrochloride (grade B, CalBiochem), pargyline hydrochloride (Abbott Labs), and sodium pentobarbital were dissolved in 0.9% saline. Doses refer to the salt. Drug concentrations were adjusted so that each bird received 1.0 ml per kg body weight. Drugs were injected into the breast muscle of the bird.

RESULTS

Control performance under the multiple FI 5, FR 30 schedule was similar to that previously reported for this schedule of reinforcement (e.g., Ferster and Skinner, 1957; Heftetz and McMillan, 1971). The mean response rate was 0.51 responses/s in FI 5 and 2.05 in FR 30 components (Fig. 1). FI responding showed the characteristic positively accelerated pattern of responding, indicated by a QL of 0.51 (Fig. 1). FR 30 responding was characterized by a brief initial pause, followed by a high and relatively constant rate of responding. There was no apparent difference in either control responding or in the sensitivity to drugs for the two breeds of pigeons used.

Pargyline produced dose-related decreases in all measures of the pattern and rate of responding (Fig. 1). FI responding appeared somewhat more sensitive than FR behavior to pargyline in that a 20 mg/kg dose decreased FI rates to about 50% of control and did not change FR rates. At 50 mg/kg, FI rates were at or close to zero, while FR rates were not as completely suppressed. One of the six birds failed to recover from the 50 mg/kg dose and died 3 days later. The other five birds recovered to control values within a few days.

Daily injections of pargyline (25 mg/kg, every 12 h) resulted in the development of tolerance to the effects of pargyline (Fig. 2). Pargyline initially decreased FI and FR response rates and QL value. Similar to the