Abstract. Sprague-Dawley male rats responding for sweetened milk on a variable interval 20 s schedule of reinforcement were trained to discriminate which of two levers to press on the basis of whether they had been injected with 1.0 mg/kg of d-amphetamine or saline prior to daily training sessions. Following acquisition of the discrimination a dose-response generalization function was determined by testing animals on 0.10, 0.15, 0.25, 0.35, 0.50, and 0.75 mg/kg of amphetamine. Subjects then received either three electroconvulsive shock (ECS) treatments or sham-ECS. Forty-eight hours after the final treatment all subjects were injected with 0.25 mg/kg of amphetamine and retested. ECS was found to enhance the ability of the animals to discriminate amphetamine. In a second experiment it was found that ECS also facilitated the ability of animals to discriminate the cue properties of apomorphine, a direct dopamine receptor agonist. These results suggest that dopamine receptor sensitivity is altered by electroconvulsive shock.

Key words: Amphetamine — Apomorphine — Discriminative stimulus — Electroconvulsive shock.

The present study used the ability of rats to discriminate amphetamine from saline in a further attempt to characterize changes in DA function following ECS. Previous investigators have demonstrated that cues used to discriminate amphetamine from saline are centrally mediated rather than peripheral (Silverman and Ho 1977) and that these cues are mediated by DA mechanisms (Schechter and Cook 1975; Kety et al. 1967), increased monoamine oxidase levels (Pryor and Otis 1975), and enhanced tyrosine hydroxylase activity (Musacchio et al. 1969) have been suggested as the primary biochemical changes underlying alterations in affect observed subsequent to ECS. More recently, it has been suggested that changes in dopamine (DA) receptor sensitivity occur following ECS (Green et al. 1977; White and Barrett 1980), adding yet another dimension to theories of biogenic amine mediation of affective change subsequent to ECS (Kety 1974).

There is controversy in the literature, however, regarding the nature of the DA receptor alteration observed following ECS treatments. Behavioral studies including enhanced circling behavior in nigro-striatal lesioned animals injected with methamphetamine or apomorphine following a series of ECS (Green et al. 1977) and the similar pattern of change in intracranial self-stimulation observed subsequent to ECS or a treatment known to produce DA receptor supersensitivity (White and Barrett 1980) suggest that ECS produces a hypersensitivity of DA receptors. Pandey et al. (1979) in a ligand binding study, however, report no change in DA receptors subsequent to ECS. While the behavioral and biochemical investigations suggest different ECS effects, a variety of procedural differences makes direct comparison difficult. Nevertheless, it is conceivable that various changes in DA receptor states can be identified following ECS depending on the exact treatment parameters employed and the temporal intervals chosen to assess ECS-induced alterations. A further explanation for the apparent discrepancy between behavioral and biochemical ECS studies is the possibility that the investigation of anatomical sites where no alteration in DA receptor sensitivity has been demonstrated is not specific to those areas primarily responsible for mediating the behavioral measures.

The present study used the ability of rats to discriminate amphetamine from saline in a further attempt to characterize changes in DA function following ECS. Previous investigators have demonstrated that cues used to discriminate amphetamine from saline are centrally mediated rather than peripheral (Silverman and Ho 1977) and that these cues are mediated by DA mechanisms (Schechter and Cook 1975; Ho and Huang 1975). For example, apomorphine, a direct DA receptor agonist, has been shown to substitute for d-amphetamine as a discriminative stimulus (Schechter and Cook 1975). Thus, if ECS alters normal DA neural activity, this change should be reflected as either an enhancement or disruption of the ability to discriminate amphetamine from saline.

Of great importance to this study is the use of amphetamine as a discriminative stimulus. Since this drug is known to produce enhanced mood in humans (Kosman and Unna 1968) and likewise has been shown in drug self-administration studies to serve as a rewarding stimulus for rats (Pickens 1968; McCown and Barrett 1980) it has been suggested that this desirable affective state serves as the discriminative stimulus associated with amphetamine (Barrett and Leith 1981). Thus, changes in the ability of the rat to discriminate d-amphetamine following ECS might represent physiological alterations that are also relevant to understanding the biological basis for the therapeutic effects of ECS in humans.

An additional goal of the present study was to determine whether changes in discrimination following ECS represent modification of pre-synaptic or post-synaptic DA processes. Since amphetamine is known to effect DA function in a...
variety of ways, including release from storage vesicles and inhibiting re-uptake into pre-synaptic stores (Creese and Iversen 1975), apomorphine, a direct DA receptor agonist previously shown to substitute for the cue properties of amphetamine (Schechter and Cook 1975), was used to further characterize ECS effects on the DA system.

Materials and Methods

Subjects. Thirty-one male Sprague-Dawley rats (Harlan Industries, Indianapolis, USA) weighing approximately 220–250 g at the onset of the experiment were housed in individual cages and food deprived to 75 ± 5% of their expected free-feeding weight. They were maintained on a 12 h light-dark cycle (7.00 a. m. – 7.00 p. m. light) and given enough food (Purina Lab Chow) immediately following each test session and on weekends to maintain their control weight throughout the experiments. The animals had free access to water. Testing occurred at the same time each day, 5 days per week.

Apparatus. Five commercially available operant chambers (BRS/LVE model No. RTC-022) each housed in a sound attenuating chamber were utilized for training rats on the discrimination task. On the front panel of each chamber, two response levers were mounted 4.92 cm above the floor and required a 24 g force to activate. Reinforcements (Borden’s condensed milk diluted 1:1 with water) were delivered by a liquid feeder (0.06 ml) centered between the two levers. Electromechanical programming and recording equipment were located in an adjacent room. White noise was used in the experimental chambers to mask extraneous auditory stimuli. A Hans Technical Model 2C electroshock machine delivered a 100 mA 0.3 s, 60 Hz, a. c. shock through ear-clip electrodes. Electrode paste helped insure good contact between the electrode and the animal’s ears.

Acquisition of the d-Amphetamine-Saline Discrimination. Following gradual deprivation to 75% of free-feeding body weights, all rats were trained to lever press during daily 30 min sessions on a continuous reinforcement (CRF). They were given training on alternate days to each of the two levers.

Once the lever press response was acquired, the reinforcement contingency was changed to a variable interval 20 s (VI-20”) and discrimination training was initiated. Rats were injected SC 15 min prior to the start of daily 20 min test sessions with either 1.0 mg/kg d-amphetamine (salt) or 0.9% saline in 1 ml/kg volumes of solution. For half of the subjects, the right lever was designated the amphetamine-correct lever and the left lever saline-correct. This was reversed for the remaining subjects. The first 2.5 min of each session consisted of an extinction period during which lever presses were not reinforced. This allowed for daily monitoring of discrimination acquisition unconfounded by reinforcement.

In order to enhance discrimination performance, after 28 daily sessions (14 each following amphetamine and saline injections), a delay was imposed such that a response on the incorrect lever was punished by a 15 s period before reinforcements were again made available. This delay was increased to 30 s after four additional sessions, and training was continued until the average percent correct responding during the initial 2.5 min extinction period was 85% or higher following both saline and amphetamine.

Generalization of the d-Amphetamine Cue to Different Doses of Amphetamine. Once stable choice behavior was established, a dose-response function was generated during 5-min extinction test sessions, i.e., no reinforcement was available to prevent the animal from receiving discrimination training to a new drug dosage which might disrupt the original baseline discrimination. In addition to the training dose (1.0 mg/kg), six other doses were tested on 6 different days (0.10, 0.15, 0.25, 0.35, 0.50, 0.75 mg/kg). All injections were administered 15 min prior to testing. Following the 5 min test session, animals were returned to their home cage. Test days were generally preceded by a drug and a saline training day.

Amphetamine Discrimination Following ECS. From the dose-response curve (see Fig. 1) it was decided that a dose of 0.25 mg/kg of amphetamine provided a sensitive baseline (63.8% correct responding) from which changes in the animal’s discrimination ability could be observed. Animals were then divided into an ECS group (n = 17) and a sham-ECS group (n = 10) matched on percent drug-lever responding subsequent to 0.25 mg/kg amphetamine. Four animals were not assigned to either group and were to be used to replace any fatalities that might have resulted from the ECS procedure. Since no fatalities occurred, these subjects were tested with the others and subsequently used in the apomorphine experiment.

The ECS animals were administered three ECS treatments, one on each of 3 consecutive days through ear-clip electrodes (100 mA for 0.3 s). ECS parameters were chosen on the basis of pilot data which varied both the number of ECS treatments administered and the ECS test interval. Each ECS animal had to experience both tonic and clonic seizures at each shock administration in order to be included in the remainder of the study.

The ear-clip electrodes were attached to the ears of the sham-ECS animals for 45 s though no current was administered. Forty-eight hours following the last ECS or sham-ECS treatment, the animals were again tested for their ability to discriminate a 0.25 mg/kg dose of amphetamine administered 15 min prior to testing.

Generalization of Apomorphine to d-Amphetamine. Twenty animals from the previous experiment and the four untreated animals were returned to baseline training (see Acquisition of d-Amphetamine-Saline Discrimination) for a 2 week period. Training was discontinued for seven animals for reasons unrelated to treatment. Generalization of apomorphine to cues for amphetamine was then tested during 5 min extinction periods. Four doses of apomorphine were tested (0.046, 0.063, 0.093, 0.125 mg/kg). All injections were administered 15 min prior to testing. After each 5 min test session, the animals were returned immediately to their home cage. As before, test days were generally preceded by an amphetamine and a saline training session.

Effects of ECS on Generalization of Apomorphine to Amphetamine. From the apomorphine dose-response curve (see Fig. 2) it was decided that a 0.063 mg/kg dose provided a sensitive baseline (42.4% correct respond-