A comparison of the stimulus effects of codeine in rhesus monkeys under the contingencies of a two lever discrimination task and a cross self-administration paradigm: tests of generalization to pentazocine, buprenorphine, tilidine, and different doses of codeine

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Abstract. The stimulus effects of codeine were assessed in three monkeys trained to perform first under the contingencies of a cross self-administration paradigm and then under a two lever discrimination task. Codeine-trained monkeys generalized to pentazocine, buprenorphine, and codeine under both procedures in doses different from the training dose. Codeine-trained monkeys did not generalize to tilidine. These results indicate that monkeys do not behave in a qualitatively different way when presented with the study drugs under both contingencies. However, there were marked quantitative differences between the generalization effects of doses of pentazocine, buprenorphine, and codeine to doses other than that used in training between the two paradigms. Much higher doses of codeine and pentazocine, but not of buprenorphine, were necessary for inducing generalization effects in the two lever task than in the cross self-administration procedure. The possible reasons for these quantitative differences are discussed. It is concluded that the cross self-administration procedure is more sensitive for the assessment of opioid-like stimulus properties of drugs than the two lever discrimination task.

Key words: Rhesus monkey - Codeine - Generalization - Pentazocine - Buprenorphine - Tilidine

Stimulus generalization effects of drugs under the contingencies of the cross self-administration procedure as well as in two-lever drug discrimination tasks are often used to assess subjective effects of drugs in animals with the aim of classifying them as belonging to a group of pharmacologically related compounds (Overton 1968, 1971, 1972, 1982; Balster 1970). Moreover, when animals trained in both paradigms to discriminate a known dependence producing drug generalize over drugs to be studied, such effects are considered to have some prediction value as regards the dependence producing effects of those study drugs (Hoffmeister and Schlichting 1972; Winger and Herling 1982; Ator and Griffiths 1983).

So far, a direct comparison of the generalization effects of groups of drugs in both operant paradigms using the same species and the same animals has not been performed. Woolverton and Balster (1982) assessed the reinforcing properties of several local anesthetics in rhesus monkeys trained to self-administer cocaine and their discriminative effects in the rat in a two-lever operant task. They found that only local anesthetics self-administered by the rhesus monkey exerted procaine-like discriminative stimulus effects in the rat, and, vice versa, not all local anesthetics exerting procaine-like discriminative stimulus effects were self-administered by the rhesus monkey. They concluded that the two stimulus properties of local anesthetics are based on different pharmacological properties, although other variables such as species differences may play a role.

In the present study an attempt was made to assess whether such dissociation of drug generalization effects depending on the operant paradigm is also effective in a group of opioids such as codeine, pentazocine, buprenorphine, and tilidine. In order to exclude the possible influence of individual and species differences, the generalization effects of these compounds were tested in three rhesus monkeys which were trained in cross self-administration as well as in a two-lever discrimination task.

Methods

Subjects

Three female rhesus monkeys (Macaca mulatta) weighing 3.5 kg (M. 1), 4.3 kg (M. 2), and 4.6 kg (M. 3) served as experimental subjects. Under sodium pentobarbital anesthesia (30 mg/kg IV) monkeys were surgically prepared with chronic silicone rubber Vivosil catheters (outside diameter 2.2 mm, inside diameter 1.0 mm) which were passed through the vena cava to the level of the right atrium. Details of the catheterization procedure have been reported by Yanagita et al. (1965), Deneau et al. (1969), and Groß (1985).

Monkeys had previous histories of IV drug self-administration with cocaine and codeine. They had no access to drugs during the 2 months prior to the onset of these experiments.

Apparatus

General conditions. The monkeys were fitted with metal harnesses for restraint. Each monkey was housed in a cube (76 cm wide, 91 cm high, 66 cm deep) fitted with a jointed metal restraining arm which was attached to the harness and allowed the animal almost complete freedom within the cube. The front of the cube was completely open to allow observation and maintenance of the monkey, the harnesses serving as the only restraint of the animals. The
surgically implanted catheter passed subcutaneously to the back of the monkey where it left through a stab wound in the skin and then passed through the restraining arm to an infusion pump (Cole Palmer Masterflex) mounted behind the cubicle. To prevent blood from clotting in the catheter the animals received a continuous infusion of 3% heparin solution at a rate of 3 ml per h for 22 h per day.

Pellets were delivered by a motor driven pellet dispenser (Ralph Gerbrands Comp., Arlington, Mass., USA).

**Two-lever discrimination task.** Two keys (Levers, Lehigh Valley Electronics, Model 1380) and two white stimulus lights (2.4 W, placed 2 cm above the keys) were mounted on the back wall of the cubicle. The distance between the two keys and the two lights was 30 cm. To prevent monkeys from operating the two keys simultaneously (with both hands) during session time a plastic wall was mounted between the two keys. A food tray was mounted between the two keys so that the animals had access to food from either side of the plastic wall. The animals were maintained at 90–95% of their free feeding weight. In addition to food pellets (precision food pellets, 300 mg, banana flavour, Noyes Company, Lancaster, N.H.) obtained in the daily lever discrimination task each rhesus monkey was fed a ration of monkey chow approximately 6 h after the sessions.

**Cross self-administration procedure.** For cross self-administration experiments only one key and one white stimulus light remained mounted on the back wall of the cubicle. The plastic wall used for the two-lever discrimination task was not used during cross self-administration sessions.

**Procedure**

**Two-lever discrimination task/training conditions.** Each daily session of 30 min duration began with a time-out period, during which the house light (on top of the cubicle) was illuminated and lever responses were counted but had no programmed consequences. When drugs were administered the time-out period served as a time period for the drug to become effective (absorption etc.). At the end of the time-out period the house light was turned off and the two white jewel lights correlated with food pellet availability were illuminated. Food pellet delivery depended upon completion of a fixed number of consecutive responses on the lever appropriate to the drug or no-drug training condition. Completion of the response requirement turned off the white lights and operated the pellet dispenser.

Initial training was conducted on the no-drug lever and the requirement for pellet delivery was raised gradually from one to ten (FR 10) consecutive responses. When responding occurred almost exclusively on the no-drug lever training on the drug lever began. An IV injection of the training drug administered through the indwelling catheter preceded each session. For all three monkeys the training drug was 5 mg/kg codeine. Training under drug conditions continued until responding occurred almost exclusively on the drug lever.

Sessions preceded by drug were alternated with sessions not preceded by drug.

**Test conditions.** After at least 20 training sessions in which drug and no-drug conditions alternated, testing began if the performance in each of the last four sessions (sequence: codeine 5 mg/kg – saline – saline – codeine – 5 mg/kg) met the criteria that no run of ten consecutive responses had occurred on the non-reinforced lever before the first pellet delivery and 98–100% of the total ten response (FR 10) runs had been on the reinforced lever.

In test sessions ten consecutive responses on either lever produced reinforcement but in other respects test sessions followed the same procedure as training sessions.

The sequence of administration before testing novel substances was kept identical: Codeine 5 mg/kg – saline – saline – codeine 5 mg/kg – novel substance. If an animal did not discriminate correctly during this sequence and an error occurred at one of the 4 administration days (codeine or saline), the sequence was turned off and started again at the beginning.

Codeine as well as novel substances were tested in a generally descending order, starting always with the highest dose. Injection time of all drugs and doses was 1 min. Doses administered as “highest” were selected according to the tolerance of the individual drugs by the animals under the conditions of administration used in these experiments. Thus, 5 mg/kg IV codeine were tolerated without obvious side effects, whereas 6.3 mg/kg induced tremors and excitation. Pentazocine 6.3 mg/kg IV and 10 mg/kg IV tilidine were also tolerated without side effects, whereas 8 mg/kg and 12.5 mg/kg IV, respectively, of these compounds induced excitation and occasional short-lasting convulsions. Intravenous administration of doses of buprenorphine higher than 2.0 mg/kg resulted in strong sedation.

**Cross self-administration.** After completion of the drug discrimination experiments one of the two levers and one of the two stimulus lights were removed from the cubicle. Subsequently, animals were allowed to recover from experiments for 4 weeks. During that time lever pressing had no scheduled consequences.

After the end of the recovery time the three monkeys were trained to self-administer codeine in the unit dose 50 μg/kg/infusion (unit dose—dose per infusion). Initially codeine was made available 22 h per day. Each lever press produced a codeine infusion. The white stimulus light was illuminated during periods of drug availability but not during drug infusion. Once responding was maintained by codeine infusions, drug availability was limited to 3 h per day, and the number of responses required was gradually raised to ten in order to produce each infusion (FR 10). The number of codeine injections self-administered under the FR 10 schedule remained stable after 24 (18–30) days of the codeine self-administration. The average number of codeine infusions self-administered per session after this time was 103 (±23) infusions. Self-administration behavior was considered stable when the number of self-administered injections between 6 subsequent days (sessions) did not differ by more than 20%. After completion of the training period for codeine self-administration saline extinction was tested over six daily sessions in all three monkeys involved in the study with restabilization on 50 μg/kg/infusion of codeine for at least 6 days.

Subsequently, codeine (50 μg/kg/infusion) was replaced by codeine in the doses 25, 10, 1, and 0.1 μg/kg/infusion, pentazocine (250, 50, 10, and 1 μg/kg/infusion), buprenorphine (50, 10, 5, 1, and 0.1 μg/kg/infusion), and tilidine (1500, 500, and 250 μg/kg/infusion). The different doses of