A3

DISCRIMINATIVE STIMULUS PROPERTIES OF CAFFEINE: STUDIES USING PURE AND NATURAL PRODUCTS. J. M. Carney and H. Dix Christensen. Department of Pharmacology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190.

Male (Sprague-Dawley) rats were trained to discriminate the effects of orally administered caffeine (32 mg/kg) from water under a variable interval 30 sec schedule of food reinforcement. Responding on lever 1 resulted in food reinforcement only under the caffeine pretreatment condition. Lever 2 responses resulted in reinforcement only on days when water pretreatments were given. Test sessions occurred no more frequently than every third day. All generalization data were obtained under a 5 min extinction condition. A dose-related caffeine generalization occurred at doses between 3.2 and 32 mg/kg. Complete generalization was observed at 10 and 32 mg/kg caffeine. Caffeine-trained rats generalized to theophylline at 10 and 56 mg/kg. When tested by the oral route with caffeine containing beverages, rats showed a dose-related generalization to the 32 mg/kg caffeine cue. Rats correctly identified caffeine when it was orally administered in either coffee or coca cola. The results of these studies clearly demonstrate that caffeine is a discriminable compound. In addition, they point out the usefulness of drug discrimination techniques in studying the behavioral effect of natural products.

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A STRUCTURE-ACTIVITY ANALYSIS OF THE STIMULUS PROPERTIES OF TRH. J. M. Carney and Rolf Geiger. Department of Pharmacology, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190, USA and Rolf Geiger, Hoechst Aktiengesellschaft AG, Frankfurt, Germany.

Six male (Sprague-Dawley) rats were trained to discriminate between the effects of 20 mg/kg Thyrotrypin Releasing Hormone (TRH) and saline under a variable interval 30 min schedule of food reinforcement. Generalization to TRH was tested under a 5 min extinction condition. A dose-related increase in TRH correct responses occurred at TRH doses between 3.2 and 10 mg/kg. MK 771, a thienyl analog of TRH, generalized to TRH and was approximately 3 times more potent. Two metabolites of TRH, cyclo-histidyl-proline and histidyl-proline, also appeared to generalize. Amphetamine did not generalize to TRH at doses between 0.1 and 3.2 mg/kg. Acetyl-histidyl-proline did not generalize to TRH. In addition, the reverse sequence dipeptides prolinyl-histidine and acetyl-prolinyl-histidine did not generalize to TRH.

A5

CONDITIONED AVERSION TO FOOD PRODUCED IN PENTOBARBITAL-DRUGGED RATS
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The abilities of nondrugged (n=8) and pentobarbital-drugged (n=8; 25 mg/kg, i.p.) Long-Evans rats to acquire a taste aversion was investigated. All rats were habituated for 2 weeks to a 23.5-hour, food-deprivation schedule, in which they received 30-minutes of access each day to a gruel of equal parts of water and powdered chow. Drugged rats were fed as soon as they had regained their righting reflex following drug administration; nondrugged rats were fed 30 minutes after an injection of physiological saline. On the first day of aversion conditioning and every third day thereafter, rats were given grape-flavored gruel and then poisoned with lithium chloride (20 cc/kg, .15 M, i.p.). All rats received unflavored gruel on the two, intervening test days. Through five cycles of the aversion procedures, seven of eight non-drugged rats showed an aversion to grape-flavored gruel by reducing their intake of the flavored chow. In contrast drugged rats reduced intake of all food, both flavored and unflavored, to such an extent that seven of eight starved to death. The reason to suppose that these deficits represent a conditioned aversion and not a nonspecific illness was that the drugged rats reacted to all food with displays of interim activities and redirected feeding that are characteristic of rats in aversive situations and that the nondrugged rats showed when presented with grape-flavored gruel. We believe that these observations are consistent with our previous conclusions that drugged rats learn response sequences and not discriminations based on peripheral cues. Thus the drugged rats were unable to select their food on the basis of flavor differences and instead associated the response of eating, itself, with the poison, unconditioned stimulus.

A6

A PROCEDURE FOR RAPIDLY EVALUATING THE DISCRIMINATIVE STIMULUS PROPERTIES OF DRUGS. Seymore Herling, R. Young Hampton, Albert J. Bertalmio, Gail Winger, and James H. Woods. Departments of Pharmacology and Psychology, University of Michigan, Ann Arbor MI 48109.

Rhesus monkeys were trained to emit 100 consecutive responses (fixed ratio 100: FR 100) on one of two levers after a subcutaneous injection of drug and the same number of consecutive responses on the other lever after a sham injection. The completion of each FR 100 was followed by the delivery of 3 g of food. Daily sessions consisted of 2-6 discrete FR 100 trials, each separated by 10 min. The appropriate lever for a given trial, except for the last trial of the session, was determined by the injection (i.e., drug or sham) that the animal received 10 min prior to the start of the trial. During training sessions, some number of sham-lever appropriate trials (0-4) always preceded two consecutive drug-lever appropriate trials. An injection of drug preceded the first drug trial and a sham injection preceded the second "drug" trial. During training, the trial in which the animal received the drug injection varied unsystematically. During tests of stimulus generalization to other drugs, animals received an increasingly larger cumulative dose of the test drug 10 min prior to the start of each successive trial. During these trials, 100 consecutive responses on either the drug-appropriate or sham-appropriate lever resulted in food delivery. A test session usually continued until more than 90% of the responses during a trial were distributed on the drug-appropriate lever or until the rate of lever pressing was markedly suppressed. In this way, a complete dose-effect curve for a test compound was usually determined within a single daily session. We have used this procedure to evaluate the stimulus properties of drugs in less than one-third the time it takes to generate comparable data using procedures that evaluate only a single dose of a drug per test session. Supported by USPHS Grants DA 00154, DA 00254, and DA 02230.

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EFFECTS OF DOSAGE ON DISCRIMINATION OF MORPHINE FROM SALINE
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Rats were trained to make differential responses in a two-lever chamber by food reinforcement for pressing one lever at 30 minutes after morphine (s.c.) and for pressing the alternative lever after saline. Three groups received different doses of morphine (8, 4 or 2 mg/kg). After 24 training sessions, each group was tested with novel doses of morphine and at novel times after administration of its training dose. Following the first series of tests all groups were given 16 additional training sessions, with half the prior training doses of morphine, followed by another series of tests with morphine doses. In the first series of tests the ED50 was 3.3, 2.5 and 1.1 mg/kg respectively after training with 8, 4 and 2 mg/kg. In the second series of tests the ED50 was 1.5, 0.8 and 0.6 mg/kg respectively after training with 4, 2 and 1 mg/kg. These ED50 values indicate that sensitivity to the discriminative drug stimulus is enhanced by a low training dose and also in the second series of tests after the training dose has been decreased. The discriminative drug stimulus trained at 30 minutes was closely similar in tests at 20 and 60 minutes but was weaker at 5 and 10 minutes. The response rates, measured in 60-second initial intervals without reinforcement, were lower during training sessions after drug than saline in the group with the highest dose (8 mg/kg in the first phase, 4 mg/kg in the second phase), were decreased in all groups by doses higher than the training dose, and were generally lower in tests at shorter or longer intervals after drug injection than in the initial portion of training sessions at the 30-minute interval. The results suggest that morphine doses of 8 mg/kg and higher are behaviorally toxic and disrupt the discriminative behavior while 2 mg/kg is difficult for naive animals to discriminate from the nondrug condition. (Supported by USPHS Research Grant DA 02298 from NIDA.)