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Similar and selective actions of chlorpromazine, chlordiazepoxide and nicotine on shock-produced aggressive and anticipatory motor responses in the squirrel monkey.

G.S. Emley and R.R. Hutchinson

Fort Custer State Home, Research Dept.
and
Western Michigan University

Squirrel monkeys, studied during response-independent, periodic presentation of electric shock, engaged in biting attack behavior after shock and anticipatory manual and locomotor behavior before shock. Administration of chlorpromazine, chlordiazepoxide and nicotine produced dose dependent decreases in attack reactions and simultaneous increases in anticipatory responses. At high dosages chlorpromazine and chlordiazepoxide generally suppressed while nicotine generally stimulated both response classes. Implications of these results for understanding the behavioral mode of action of antianxiety agents and advantages of the method for drug testing are noted.

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RESEARCH DEPARTMENT

FORT CU[illegible] STATE HOME
P.O. BOX 248
AUGUSTA, MICHIGAN 49012
Phone: 616-731-4183

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Dear Sir:

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Sincerely,

Ronald R. Hutchinson

Ronald R.Hutchinson, Ph.D.
Research Director

Painful stimuli (shock, intense heat, physical blow) produce attack against members of the same species, other species and inanimate objects. The reaction has been observed in rats, hamsters, cats, and squirrel monkeys (Ulrich, Hutchinson & Azrin, 1965: Azrin, Hake & Hutchinson, 1965).

Attack occurs immediately after the aversive stimulus and then progressively decreases. Stimuli associated with or occurring prior to painful or aversive events can also produce locomotor and manual behaviors which may or may not alter the noxious event (Brogden, Lipman & Culler, 1938). Where noxious events occur repetitively, both aggressive and anticipatory motor reaction classes can be simultaneously studied (Hutchinson, Renfrew & Young, 1971). In these later studies, a periodic, response-independent shock presentation program produced biting attack immediately after shock and lever-pressing before shock, but general suppression of all behavior immediately prior to shock. Effects of several drugs on these topographically and temporally distinct behaviors have been reported (Hutchinson & Emley, 1970). While d-amphetamine caused parallel increases in both behaviors and morphine caused parallel decreases, chlorpromazine increased pre-shock motor behaviors, but decreased post-shock attack behavior. This report presents results of testing two additional drugs, chlordiazepoxide and nicotine, both of which produce differential effects on attack and anticipatory motor responses.

METHOD

<u>Subjects</u> Subjects were seven, adult, squirrel monkeys (3 females: HC-26, -28,-29) weighing 5[illegible].0 to 8[illegible] grams. Subjects were housed separately,

had free access to water, and were fed Wayne monkey diet.

Apparatus Restraint chairs (Plas Labs), equipped with a response lever (LVE #1532) and tail electrodes were used. A latex rubber bite hose mounted on the front panel of the chair was connected to an Air Switch (Tapeswitch Corp.) which was calibrated to record only bite attacks. The chairs were enclosed in sound attenuated, ventilated chambers.

Procedure During each 64-minute session, 15 tail shocks (20 ms, 4[illegible] v AC) were delivered on a 4-minute, periodic schedule. Hose bites and lever presses were recorded on counters and cumulative recorders. These conditions were continued for at least two months before the drug administration.

Drug Administration Compounds were prepared with physiologic saline and injected subcutaneously in a constant volume. Chlorpromazine (0.06, 0.12, 0.25, 0.5, 1.0, 2.0 mg/kg) and chlordiazepoxide (0.25, 1.5, 1.0, 2.0, 4.0, 8.0, 16.0, 24.0, 32.0 mg/kg) were given 3[illegible] minutes prior to the session. Nicotine (0.02, 0.04, 0.08, 0.16, 0.32, 0.64, 0.8, 1.0, 1.2, 1.4, 1.6 mg/kg) was given 5 minutes prior to the sessions. Drugs were given in a mixed order of dosages on Wednesday of a five day experimental week. Saline injections were given on the other four days.

RESULTS

In Figure 1, the upper graph for each subject on each drug shows the ratio of lever presses to total resopnses (lever presses plus bites) at each dosage of chlorpromazine, chlordiazepoxide and nicotine. The dotted line represents the ratio for the saline control testing. The lower graph for each subject on each drug shows the total responses (solid dots) at each dosage and the saline control (solid line), and lever presses (open dots) and the saline control (dotted line).

All three drugs have a selective effect on lever presses relative to biting attack responses. Though the ratio of lever presses to total responses increases with increasing dosage for all drugs, differences between compounds can be noted. For chlorpromazine and chlordiazepoxide, total responses decrease with increasing dosage, while for nicotine, total responses of two subjects increase at the highest dosages.

DISCUSSION

Reports have shown that viciousness, or aggressive and attack reactions are reduced by chlorpromazine, chlordiazepoxide (Randall, 1961, Heise & Boff, 1961) and nicotine (Silverman, 1969). Further manual or locomotor reactions prior to shock (often studied during avoidance, conditioned suppression or punishment programs) are reported to increase under chlorpromazine (Dinsmoor & Lyon, 1961), chlordiazepoxide (Randall, 1961) and nicotine (Davis& Kensler, 1968, Pradhan, 1970). The present findings confirm these reports and extend them by showing that these different effects of the same drug may be obtained simultaneously from the same subject during a single test session and at a single drug dose. The differential changes in responding observed with the present method control against the uncertainty of general depressions or elevations of behavior often inherent in single response paradigms.

The present data suggest that the therapeutic nature of these compounds may perhaps result from a shift in behavioral tendencies from post-event irritability and aggressivity toward an increase in anticipatory locomotor and manipulative reactions.

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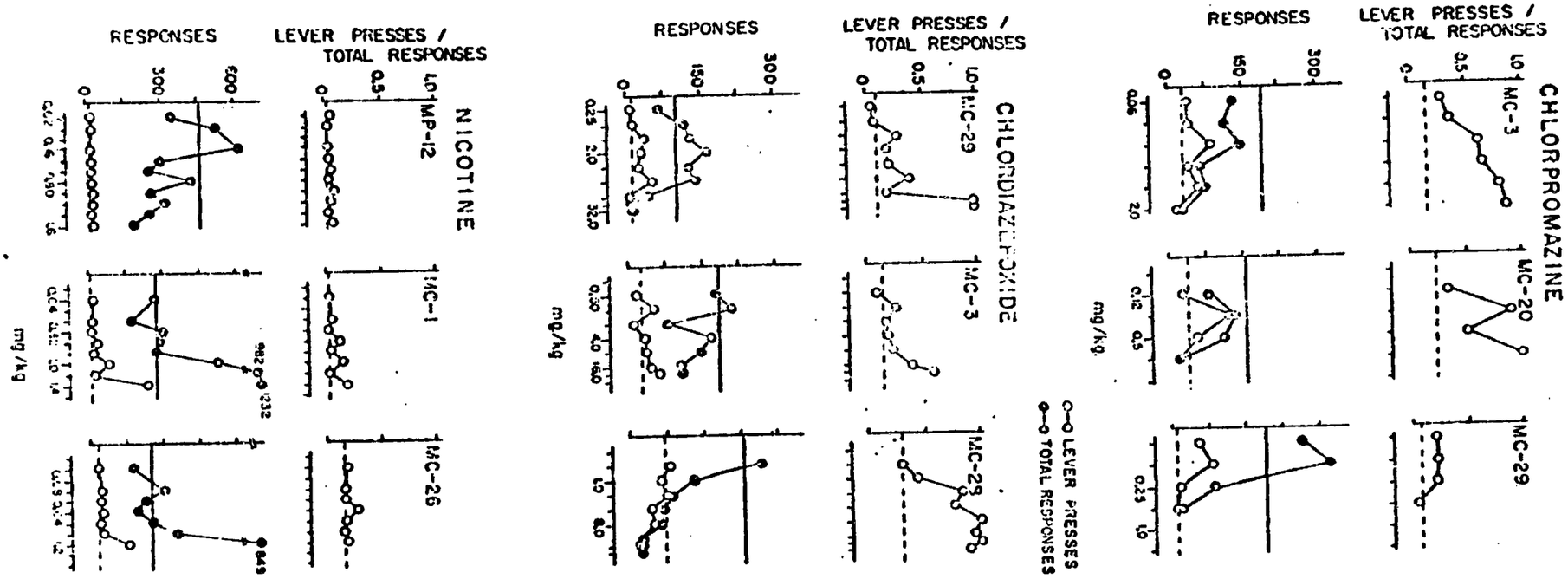

Figure 1

Lever presses and total responses of 3 subjects after chlorpromazine, chlordiazepoxide and nicotine administration. Saline control in the upper graphs is represented by the solid lines, and dotted lines (lever presses) and solid lines (total responses) in the lower graphs.