The extension of alcohol-induced behavioral deficits with pyrazole

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Shuttlebox avoidance and fixed-ratio operant responding in rats are adversely affected, but not disrupted, by ethanol injections (2.5 g/kg and 1 g/kg, respectively) given 15 prior to test. The recovery of these impairments was retarded absolutely up to 2 h by 24 h prior injections of pyrazole (4.3 mmol/kg). The results are discussed as they related to differing central nervous effects of alcohol.

Pyrazole and its derivations are known to inhibit ethanol metabolism by way of their action on liver alcohol dehydrogenase (Theorell and Yonetani, 1963; von Wartburg, 1971). Lester and Benson (1970) were able to show that ethanol oxidation was inhibited as much as 34% for as long as 66 h after a 6.6-mmol/kg pyrazole injection in rats. This dosage was found to reduce the voluntary intake of alcohol by rats for as long as 24 h after injection (Erspamer & Crow, 1972).

By use of a tilting plane, Goldberg and Rydberg (1969) found that not only did pyrazole extend the duration of intoxication in rats, but also produced a synergic interaction with alcohol potentiating the impairment. These authors did not look at more complex or learned behaviors, however, and the properties of pyrazole would appear to lend themselves to a comparative study of the continued presence of alcohol in the blood upon relatively simple, as opposed to complex, skills. Under the unusual circumstances in which a drug-induced sensory or motor impairment remains relatively constant, it seems possible that compensatory processes of higher nervous activities may be at work in highly practiced skills. The present study was undertaken to assess the effect of prolonged intoxication through pyrazole upon complex behaviors by use of an alcohol dosage which would detectably interfere with, but not disrupt, performance.

METHOD

Subjects

Forty experimentally naive Holtzman albino rats were used. The animals were all males approximately 90 days of age at the beginning of their use in each study.

Apparatus

The avoidance conditioning was carried out in a shuttlebox which was 26.7 cm high, 19 cm wide, and 30.4 cm in length. A spring-loaded barrier, 3.8 cm high, separated the independently electrifiable grid floors. Fifteen-watt light bulbs were located on the ceiling on each side to serve as conditioning stimuli. Shock was delivered through a grid scrambler at an intensity of 1 mA. The operant-conditioning apparatus was a modified Grason-Stadler module in conjunction with Gerbrands ratio programmers.

Dosages

Alcohol dosages of 2.5 g/kg for the avoidance and 1 g/kg for the operant conditioning were administered intraperitoneally from a 24% solution of 95% ethyl alcohol and saline solution. Pyrazole dosages of 4.3 mmol/kg for the conditioned avoidance and both 4.3 mmol/kg and 3.3 mmol/kg in operant conditioning were delivered intraperitoneally from a molar solution of pyrazole (J. T. Baker Chemical Co.) in saline.

Procedure

In both the avoidance and operant-conditioning situations, animals were first trained to a stable level of responding in terms of the measures: percent avoidances and *time on bar* which was the mean time in seconds of barpressing duration with a fixed-ratio reinforcement schedule (O'Kelly, 1962). In avoidance conditioning, animals were run in sessions of 50 min for 100 trials at an intertrial interval of 30 sec, using a 5-sec interstimulus interval (Crow, 1966). In operant conditioning, animals were run daily for 30 min after adaptation to a 23.5-h water-deprivation schedule, and trained successively to fixed ratio 20:1 (O'Kelly et al., 1966).

In the case of conditioned avoidance, 18 animals were divided into four groups: (1) Alcohol zero delay group. Three animals were run 15 min after the alcohol injection (2.5 g/kg) with no previous treatment. (2) Alcohol-pyrazole group. Five animals received pyrazole injections followed 24 h later by alcohol injections, and were tested 2 h subsequently. (3) Alcohol-placebo group. Five animals received a placebo (isotonic saline) injection followed 24 h later by an alcohol injection and were tested 2 h subsequently. (4) Pyrazole control. Five animals were injected with pyrazole followed 24 h later by a placebo injection, and run 2 h later.

In operant conditioning, 22 animals were run in the following conditions: Alcohol zero delay. Eighteen animals, both with and without a 24-h-prior pyrazole treatment (3.3 mmol/kg) were tested 15 min after alcohol injections (1 g/kg). All animals were run in each condition accounting for order of treatments. Four animals were run through all sequences represented in the conditioned avoidance treatment groups above using in this case the pyrazole dosage of the avoidance study (i.e., 4.3 mmol/kg). Thus, an alcohol-pyrazole session, an alcohol-placebo session, and a pyrazole-control session were carried out for each animal with all treatment orders represented.

RESULTS

Figure 1 shows the results of the conditioning of avoidance responses in the 2-h-delay conditions with the last training day or baseline data for these animals included for comparison. Analysis of variance for the

Figure 1. Percent avoidance in 100 trials of shuttlebox responding for three groups of five animals. The data from the last training session are included for reference. Range brackets indicate individual differences. Circles are mean values.

three conditions under each of the pre- and posttest sessions (Lindquist Type II, Lindquist, 1953) yields significant ($\alpha .05$) conditions effects ($F = 31.84$, $df = 12,2$) and a significant interaction of Conditions by Sessions ($F = 31.71$, $df = 12,2$). Duncan multiple-range tests show a significant difference ($\alpha .05$) in percent avoidances between the alcohol-pyrazole and all other groups, while there are no significant differences between any of the other groups in Figure 1. The alcohol zero delay group (not shown in Figure 1) differs significantly (Mann-Whitney U tests) from the alcohol-placebo and the pyrazole control groups ($p = .018$, $.018$), but does not differ significantly from the alcohol-pyrazole group ($p = .071$).

Eighteen animals were trained to respond to a fixed-ratio of 20:1 and tested at zero alcohol delay intervals (15 min after injection) both with and without prior pyrazole treatment. The time-on-bar data showed a significant alcohol effect ($\alpha .05$) by related t test ($t = 2.125$, $df = 16$) when compared with their placebo-treatment performance, and there were no significant differences between the alcohol treatment alone and the alcohol-pyrazole treatment.

Figure 2 shows a summary of the time-on-bar data for the four animals, the repeated measures on which correspond to the treatment groups of the conditioned-avoidance study above. The effects appear similar to those of Figure 1 as the alcohol-pyrazole condition or session is associated with an elevated response duration while the control sessions differ little from each other. Response-rate data closely parallel the time-on-bar data and are thus omitted in this report.

DISCUSSION

Under the conditions of the present study, prior

pyrazole treatments extended undiminished the alcohol-induced impairment of complex behaviors motivated by both shock avoidance and thirst. No impairments due to pyrazole alone were noted, and the effects appear to be dependent solely upon the continued presence of alcohol within the animal. The findings are in keeping with those of Goldberg and Rydberg (1969) using a comparatively simple righting reflex response. Contrary to the findings of the latter authors, however, was the lack of a synergic effect of pyrazole and alcohol in the present study which appears to be due to the complex or learned nature of the tasks employed.

For each learning task, the alcohol dosage was chosen so as not to produce a complete disruption of behavior, but, at the same time, to produce a discernible impairment. In the face of what was in some cases a rather severe motor impairment, the higher nervous activities of learning were at least operative. That the primary motor impairments increased during the pyrazole-induced extension of the alcohol effect seems likely on the basis of the findings by Goldberg and Rydberg (1969) and yet these augmented impairments were not discernible in the complex learning task. It is then possible that compensations at a higher central level for the motor impairments did occur, and even though performance was diminished throughout the pyrazole-induced extension of intoxication, there was no greater impairment imposed over that of the more common effects of alcohol. That limited behavioral

Figure 2. Mean time per response in operant fixed-ratio 20:1 reinforcement scheduling under four differing conditions. Range brackets show individual variation. Circles are means of four animals.

adjustments may be made to prolonged or repeated debilitation through alcohol seems likely, and the results of the present study appear to support that contention.

REFERENCES

- Crow, L. Effects of alcohol on conditioned avoidance responding. *Physiology and Behavior*, 1966, 1, 89.
- Erspamer, R., & Crow, L. A depression of ethanol consumption in rats as a result of intraperitoneal injections of pyrazole. *Psychonomic Science*, 1972, 26, 29.
- Goldberg, L., & Rydberg, U. Inhibition of ethanol metabolism in vivo by administration of pyrazole. *Biochemical Pharmacology*, 1969, 18, 1949.
- Goldberg, L., Hollstedt, C., Neri, A., & Rydberg, U. Synergistic action of pyrazole on ethanol incoordination: Differential metabolic and central nervous effects. *Journal of Pharmacology*, London, 1972, 24, 593-601.
- Lester, D., & Benson, G. Alcohol oxidation in rats inhibited by pyrazole, oximes and amides. *Science*, 1970, 169, 282.
- Lindquist, E. *Design and analysis of experiments in psychology and education*. Boston: Houghton Mifflin, 1953. P. 273.
- O'Kelly, L. Personal communication in G. Thomas. *Neurophysiology of learning. Annual Review of Psychology*. Palo Alto: Annual Reviews, 1962. P. 75.
- O'Kelly, L., Crow, L., Tapp, J., & Hatton, G. Water regulation in the rat: Drive intensity and fixed ratio responding. *Journal of Comparative and Physiological Psychology*, 1966, 61, 194.
- Theorell, H., & Yonetani, T. Liver alcohol dehydrogenase-DPN-pyrazole complex: A model of a ternary intermediate in the enzyme reaction. *Biochemistry*, 1963, 338, 537.
- von Wartburg, J. The metabolism of alcohol in normals and alcoholics. In B. Kissin and H. Begleiter (Eds.), *The biology of alcoholism*. New York: Plenum Press, 1971. P. 81.

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