Alcohol and Caffeine in Choice-Discrimination Tests in Rats. (26878)

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It is a popular belief that caffeine is an effective antagonist to alcohol. This is undoubtedly based on the generalization that alcohol is a central depressent while caffeine exerts a stimulant action centrally. Despite the apparent "stimulation" from alcohol which is evident in some persons, biological scientists agree that, if classification is essential, ethanol must be categorized as a depressant.

However, both hypnotics and tranquilizers are also central depressants. The mechanism of action, herein, as well as end results are very different and terminology such as stimulant or depressant drug is becoming meaningless.

Popular usage of the term tranquilizer often suggests that alcohol has such properties. This has been challenged since a tranquilizer should reduce anxiety without greatly obtunding other behavioral responsiveness (1). We have shown that alcohol will diminish anxiety but does so only at the expense of various parameters of performance and behavior(2,3,5).

This study was begun in order to measure the effect of alcohol-caffeine combinations on performance in the rat. It was anticipated that caffeine might reverse some of the effects of alcohol since this is so commonly reported.

Materials and methods. The experimental technique employed a shock-avoidance box (Fig. 1) in which a choice must be made for escape(1,2,3,4). The floor of the main compartment (A) consists of stainless steel rods. A warning light (L) serves as a conditioning stimulus and is presented 5 seconds before a shock is delivered *via* the grid flooring. The door (D) is lifted simultaneously with the warning light to expose the escape compartments (B) and (C). If the rat fails to escape, 5 seconds later he receives a 5-second shock delivered by the grid floor. The rat may escape to a *safe* and darkened area (B) with insulated non-shock floor, or to an *unsafe* illuminated area (C) with a grid floor that will deliver shock.

The only animals used in this study were those that had learned to respond with 100% accuracy to the "anxiety-producing" warning light by escaping to the *safe* area (B), thus avoiding shock. When the rat observes and reacts to the warning light, we consider this to be a simple conditioned avoidance response (CR). If the rat fails to leave the main compartment during the 5 seconds in which the light is on, a shock of 15v A.C. from a relatively low resistance power supply is applied to the grid for 5 seconds. If this is effective and the animal leaves the main compartment, this is recorded as an unconditioned avoidance response (UR). With our apparatus, the rat must make a decision-choice (discrimination) of the correct compartment into which he must flee. We recorded errors in discrimination as incorrect choices of compartment after a stimulus of light or of shock.

Weanling male rats were trained 3 times daily and at each testing period received 3 trials. With this 9-trial daily testing period, 90 to 95% of the animals learned to escape properly with 100% accuracy in 4 days.

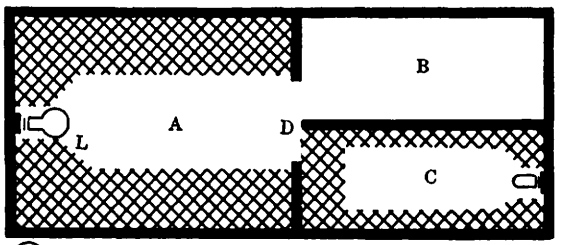
All drugs were administered intraperitoneally. Alcohol was administered as a 5% solution. Caffeine was administered as the citrate salt but calculated as 50, 100 or 150 mg/kg of body weight of the base.

After administration of the alcohol, caffeine or alcohol-caffeine combinations, the animals were tested 3 times every 15 minutes for 4 hours thereafter. Dosage levels were: 50 mg/kg, 100 mg/kg, and 150 mg/kg of caffeine, 1 g/kg of ethanol, and 1 g/kg of ethanol combined with 50, 100, or 150 mg/kg of caffeine. A control group of rats received only saline injections. Each of the total of 90 rats was used for only one 4 hour test and discarded at the end of the test period. The dosage of ethanol was selected because previous reports from our laboratory indi-

cated that this induces only a moderate effect on diminishment of performance(3). Larger doses may cause gross immobility of the animal. Preliminary studies indicated that 5, 10 or 25 mg/kg of caffeine effected no significant change in responsiveness in the animals. Therefore, 50 mg/kg of caffeine was used as the low dosage level.

Results. Total scores for the animals for each hour are represented graphically in Fig. 2, 3, 4. The control group of 10 rats continued to respond correctly, *i.e.*, no suppression of total conditioned responses. A small dose of caffeine caused no significant reduction in conditioned responses. The intermediate dose (100 mg/kg) effected a moderate reduction in conditioned responses for the first 2 hours only. A large dose (150 mg/kg) of caffeine caused a marked reduction in CR which lasted longer than the 4 hour period. Alcohol alone (1 g/kg) caused a slight (5%) reduction of CR during the first hour. However, when alcohol was combined with caffeine, the rats were markedly affected in that a greater reduction in conditioned responses resulted than could be explained by addition of the 2 drugs. There was no drug antagonism demonstrated by this "stimulant-depressant" combination. Thus, potentiation was most evident when an intermediate dosage of caffeine was combined with alcohol.

A like set of results was obtained for the



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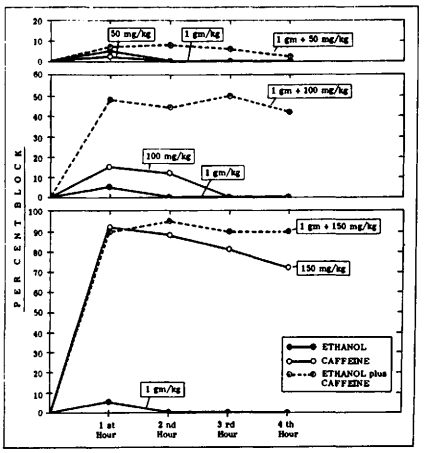

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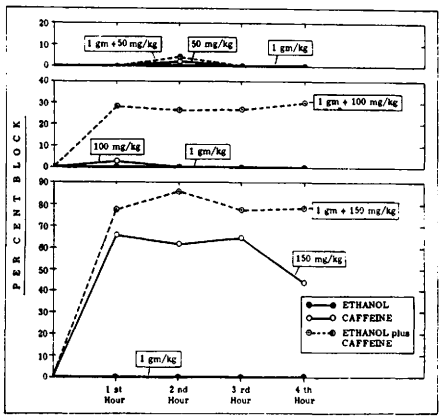

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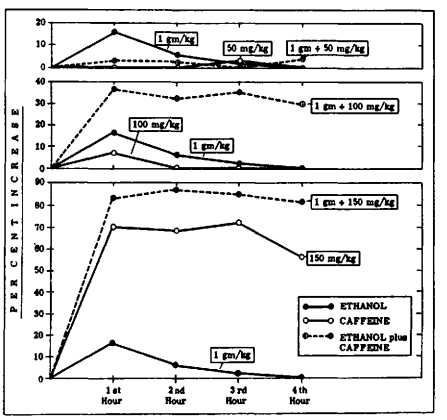

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FIG. 1. Apparatus and training method. A, main compartment: warning light, shocking grid floor. B, safe escape area: not illuminated, insulated floor. C, unsafe escape area: illuminated, shocking grid floor. D, Guillotine-type door. L, warning light.

FIG. 2. Suppression of conditioned responses in rats after alcohol, caffeine and alcohol-caffeine combinations.

FIG. 3. Suppression of unconditioned responses in rats after caffeine, alcohol and caffeine-alcohol combinations.

FIG. 4. Increase in errors in choice-discrimination in rats after alcohol, caffeine and alcohol-caffeine combinations.

unconditioned response (Fig. 2). Once again alcohol-caffeine combinations gave greater depression of responses than simple addition can explain.

Similarly, an increase in errors of choice of exits (discrimination) was observed after caffeine and alcohol were combined (Fig. 4). The rats were not noticeably stimulated by 50 or 100 mg/kg of caffeine or depressed by the alcohol alone. However, when 100 mg/kg of caffeine and 1 g/kg of ethanol were administered to the animals, an obvious depressed state resulted. The animals receiving this combination were able to respond to the unconditioned shocking stimulus but did so in a confused manner and with a large number of errors. This potentiation was also evident in the animals' receiving larger doses (150 mg/kg) of caffeine.

Discussion. An intraperitoneal injection of 1 g/kg of ethanol will effect a peak blood level in rats of approximately 90 mg% in 15 minutes and this will have largely disappeared from the blood within 2 hours(3). In the present study the effect of alcohol had disappeared by the second hour. This dose of alcohol did not produce behavioral changes such as drowsiness, reduction in activity or agressiveness. Caffeine in a dosage of 100 mg/kg i.p. altered behavior which returned to normal at the end of 2 hours. With this dosage of caffeine, some of the animals showed some hyperexcitability when handled.

The above dose of alcohol (1 g/kg) combined with caffeine (100 mg/kg) produced an effect in behavioral responses which was still present at the end of 4 hours. These animals were grossly depressed. Activity was not measured but was obviously reduced at the end of 4 hours, although the animals that received either drug alone appeared to be unaffected. The degree of gross depression seems to correlate with the reduction in behavioral responsiveness measured. It is apparent from the data that alcohol altered the behavior in such a manner that recovery was not complete although blood levels might indicate otherwise. There is evidence that recovery had scarcely begun when zero blood levels of alcohol had been reached.

The same potentiation is apparent when higher dosages (150 mg/kg) of caffeine were used but this concentration of the alkaloid is grossly depressant by itself.

It was not evident from our studies that caffeine antagonized alcohol. Rather it appears that caffeine potentiates the slight depression of conditioned and unconditioned responses due to this dosage of alcohol as well as markedly increasing errors in discrimination.

Studies in human subjects are in progress to test the hypothesis that alcohol produces behavioral degeneration which remains long after the alcohol has disappeared from the blood and that certain drugs, including stimulants, may exaggerate this effect.

Summary. A series of rats received alcohol, caffeine, or alcohol-caffeine combinations. Conditioned and unconditioned responses as well as erors in choice (discrimination) were measured. No significant changes were noted in total conditioned or unconditioned responsiveness with small doses of caffeine (50 mg/kg) or with a dosage of 1 g/kg of ethanol. By all measurements, as well as observation, caffeine potentiated the depressive effect of alcohol long after the alcohol had disappeared from the blood. This was most marked with intermediate (100 mg/kg) or with high (150 mg/kg) dosages of caffeine. In no instance did caffeine antagonize the effects of alcohol.

1. Hughes, F. W., Kopmann, E., *Arch. de Pharmacodyn. et de Therap.,* 1960, v126, 158.

2. Kopmann, E., Hughes, F. W., *A.M.A. Arch. Gen. Psychiat.,* 1959, v1, 7.

3. Hughes, F. W., Rountree, C. B., *Arch de Pharmacodyn. et de Therap.,* 1961, in press.

4. Kopmann, E., Hughes, F. W., *Experientia,* 1958, v14, 8.

5. Forney, R. B., Hughes, F. W., *J. Psychol.,* 1961, v52, 185.

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