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Effects of Pentobarbital and Cocaine in Rats Expecting Pentobarbital

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HINSON, R. E., C. X. POULOS AND H. CAPPELL. *Effects of pentobarbital and cocaine in rats expecting pentobarbital.* PHARMAC. BIOCHEM. BEHAV. **16**(4) 661–666, 1982.—Rats received extensive exposure to pentobarbital in a distinctive environment, and were subsequently tested for tolerance to the sedative effects of pentobarbital either in the distinctive environment or in an environment previously associated only with saline. Rats tested when expecting pentobarbital (i.e., in the usual drug environment) were tolerant, but rats tested when not expecting the drug (i.e., in the saline environment) were not tolerant. These results extend demonstrations of conditional tolerance to the general behavioral arousal effects of a sedative hypnotic. Subsequently, the same rats were administered cocaine either when expecting pentobarbital or when not expecting pentobarbital. Rats administered cocaine when expecting pentobarbital exhibited more intense forms of cocaine-induced behavior than rats administered cocaine but not expecting pentobarbital. These results establish the phenomenon of conditional cross-potentiation between conditional drug states and unconditional drug-effects.

Pentobarbital Cocaine Conditional drug states Tolerance Cross-potentiation Pavlovian conditioning

IT has been suggested that Pavlovian conditioning processes contribute to tolerance [7, 17, 19]. A role of conditioning in tolerance is based on Pavlov's [15] suggestion that the administration of a drug normally conforms to the operational specifications of a classical conditioning trial: Environmental stimuli regularly preceding drug administration serve as conditional stimuli (CSs) for the actual drug effects, which constitute the unconditional stimulus (UCS). Repeated drug administrations in conjunction with the same set of predrug stimuli lead to the development of an association between the environmental CS and pharmacological UCS. This association manifests itself as a conditional response (CR) which is opposite in direction to the actual drug effects [19], and hence Pavlovian conditioning may contribute to tolerance because drug-opposite CRs act to cancel drug effects.

On the basis of the conditioning interpretation of tolerance, organisms with a history of drug administration should display more tolerance when administered the drug in the context of stimuli previously associated with the drug than when the drug is administered in the context of novel cues, or cues previously paired only with the administration of an inert substance. That is to say, tolerance should be maximally displayed following "expected" drug administration but not following "unexpected" drug administration [7,21]. There are, in fact, several demonstrations that such drug expectations affect the display of tolerance to the effects of morphine [19, 20, 21], alcohol [7], pentobarbital [2], heroin [22], and amphetamine [19]. Further, there is direct evidence for conditioning of drug-opposite responses: When a drug-tolerant animal expects a drug, but the drug is not administered, the animal often exhibits drug-opposite responses. However, animals with the same drug experience do not evidence the drug-opposite responses unless confronted with the conditional predrug stimuli [7,20].

Most of the research dealing with the effects of drug expectation in tolerance has involved exposing animals to only a single drug. A recent experiment [2] has, however, demonstrated that the expectation of one drug effects responsiveness to a different drug. Rats were made tolerant to the hypothermic effect of pentobarbital by repeated injections of the drug in conjunction with a distinctive set of stimuli. Subsequently, these barbiturate-tolerant rats were administered a test dose of ethanol which also produces hypothermia. For half these animals, the ethanol test occurred under conditions where they expected pentobarbital; for the other half, under conditions where they had previously received only saline and thus did not expect pentobarbital. Rats administered ethanol when expecting pentobarbital were cross-tolerant; rats receiving ethanol when they had no expectation of pentobarital were not. The Pavlovian analysis of cross-tolerance is the same as for tolerance: Tolerance to pentobarbital hypothermia results because predrug stimuli elicit a drug-opposite hyperthermic response. This drug-opposite CR serves to cancel any drug effect simi-

lar to that produced by the original tolerance-inducing drug (e.g., cross-tolerance between pentobarbital and ethanol hypothermia).

Pavlovian theory predicts conditional control of cross-tolerance when the conditional response to drug "A" is in a direction opposite to the acute effects of drug "B." In this circumstance, the algebraic combination of a conditional response and an acute drug effect with opposite "signs" results in cross-tolerance when drug "A" is expected, but drug "B" is administered. An interesting and important question arises in a situation in which the drug-opposite CR in expectation of drug "A" and the acute effects of drug "B" are is a similar direction. In this case, the algebraic combination of the conditional drug-opposite reaction for drug "A" and the unconditional, acute effects of drug "B" would not be cancellation (cross-tolerance), but summation (cross-potentiation). Suppose that an organism were made tolerant to a CNS depressant (drug "A") in a particular environment. The conditional drug-opposite response that would come to be evoked by predrug stimuli should be CNS "stimulation." If this organism, tolerant to drug "A," were placed in the same environment but were given a CNS stimulant (drug "B"), it would be predicted that potentiated stimulation would result. This prediction is based upon a combination of conditional (opposite to drug "A") and unconditional (acute effect of drug "B") stimulation. However, if this same organism were placed in an environment never paired with depressant drug "A" and administered stimulant drug "B," only the usual stimulant effect of drug "B" should result. The demonstration of such conditional cross-potentiation is a unique prediction and an important extension of Pavlovian analysis of drug effects.

The present experiment investigated the possibility of conditional cross-potentiation between the behavioral effects of CNS depressants and stimulants. Pentobarbital is a sedative-hypnotic which has behavioral depressant effects and has been used clinically as an anticonvulsant [5]. Cocaine is a psychomotor stimulant which produces increases in activity, stereotypy, and convulsions [16,23]. In the present experiment, animals were repeatedly injected with pentobarbital, each injection occurring with a distinctive set of environmental stimuli. Animals were then tested for tolerance to pentobarbital when they either did, or did not, expect the drug. Subsequently, animals were injected with cocaine under the same conditions, i.e., when they either did, or did not, expect pentobarbital. At a general level, cocaine and pentobarbital have opposite behavioral effects. Thus, it is expected that potentiated reactions to cocaine would be observed in animals tolerant to, and expecting, pentobarbital.

EXPERIMENT 1A

Successful demonstrations of conditional tolerance to effects of sedative hypnotics such as ethanol and pentobarbital have been confined largely to thermic effects [2, 3, 10, 12, 13]. Tolerance to the general behavioral sedative effects of pentobarbital is readily demonstrable [8], but conditional tolerance to this effect has not been studied. Since conditional cross-potentiation involving general behavioral stimulation was the focus of the present research, it was necessary to first demonstrate conditional control over tolerance to the sedative effects of pentobarbital before testing for conditional cross-potentiation between cocaine and pentobarbital.

METHOD

Subjects, Drugs and Apparatus

Forty-two naive, male Wistar-derived rats (Canadian Breeding Farms, St. Constant, Quebec), each weighing between 300–400 g were individually housed with free access to water, but access to food restricted to 25 g per day.

Barbiturate injections were pentobarbital sodium. Placebo injections consisted of physiological saline. All injections were intraperitoneal. Drug concentrations were such that injections were at a volume of 1 ml/100 g.

All pretest pentobarbital injections were given in a room characterized by dim, red-light illumination and noise (75 db above 20 μ N/m^2). Pretest placebo injections were given in the same room, but the room was well-illuminated and there was no extraneous noise. During all experimental sessions, rats were individually retained in clear, Plexiglas boxes (27×27×39 cm) in the injection room.

Design and Procedure

Thirty rats received alternate daily injections of pentobarbital or placebo over a period of 146 days during an initial tolerance development phase of the experiment. For both pentobarbital and placebo injections, rats were transported from the colony room to the injection room and placed in the observation boxes. Five minutes after transport into the injection room, all rats were injected. All rats remained in the observation boxes in the injection room for 60 min following injection, after which time they were returned to the animal colony room. The first 20 pentobarbital injections were at a dose of 30 mg/kg, and the remaining 53 at a dose of 45 mg/kg. During the tolerance development phase, eight rats died, leaving 22 pentobarbital-experienced rats to enter the subsequent test phase of the experiment.

On the day following the last tolerance development session, rats were randomly divided into two groups, and administered a tolerance test involving the injection of 45 mg/kg dose of barbiturate. Twelve rats received the test injection of pentobarbital under the usual pretest drug conditions, i.e., in the darkened, noisy injection room (Expected). The remaining ten rats received the test injection of pentobarbital under the pretest saline-injection conditions, i.e., in the well-illuminated, quiet injection room (Unexpected). For the test session, each rat was transported from the colony room to its designated test injection environment and injected five minutes after being placed in the observation box. Rats remained in the observation boxes for 120 min following drug injection, thus the total session time was 125 min. During the test session, each rat's behavior was videotaped during the total 125 min.

An additional group of twelve control rats received saline injections, alternating between the two injection environments, during the initial tolerance development phase of the experiment. During the test session, six of these control rats received the 45 mg/kg test injection of pentobarbital in the darkened, noisy room, and six in the well-illuminated, quiet room. These control animals served to determine whether there were any differential nonassociative effects of the two injection environments on the acute sedative effects of the drug.

Data Treatment

The videotapes of each rat's behavior during testing were scored, by a single observer blind as to the subject's group assignment, using "sleeping time" as a measure of the seda-

tive effects of pentobarbital. Sleeping time was defined as the elapsed time between when the animal lost a righted posture and did not move, until it righted itself and locomoted. Overall data analysis was by means of a one-way Analysis of Variance, with subsequent pairwise comparisons computed using Newman-Keul's tests.

RESULTS AND DISCUSSION

The video recorder malfunctioned for two control rats and data from these animals are not included in the analysis. The mean sleeping times (±1 SEM) of the two control groups, receiving pentobarbital for the first time during testing were 105.2 min (±0.4) and 102.0 (±4.5) in the dark, noisy and quiet, light environments, respectively. The difference in sleeping time of the two control groups was not significant indicating that there were no differential nonassociative effects of the two different injection environments on the acute sedative effect of pentobarbital. Consequently, a single control group was formed for purposes of analyzing test session results.

Three animals in Group Unexpected did not recover prior to the end of the test session and were assigned maximal sleeping time of 120 min. The mean sleeping times (±1 SEM) of the two pretest pentobarbital-injected groups were 87.5 min (±3.1) and 106.2 min (±4.6) for Expected and Unexpected, respectively. The overall analysis of sleeping time indicated a significant difference among the groups, $F(2,29)=10.14$, $p<0.005$. Subsequent pairwise comparison analyses revealed that Group Expected differed significantly from both Group Unexpected and the control group (both p's $p<0.01$), but that the difference between Group Unexpected and control was not significant.

The present results clearly demonstrate a role of environmental stimuli in the display of tolerance to the sedative effects of pentobarbital: Animals in Groups Expected and Unexpected had the same pharmacological history, handling, and experience with the two injection environments, yet animals receiving an unexpected drug injection during testing remained sedated longer than animals receiving an expected drug injection. In fact, animals in Group Unexpected remained sedated during testing for as long as animals in the control group which had no pretest pentobarbital experience. Thus tolerance to pentobarbital's sedative effects was displayed only when the drug was administered in the context of stimuli which had previously signaled pentobarbital administration. According to the conditioning theory of tolerance, environmental stimuli affect tolerance because of an association between predrug cues and the drug. However, other investigators have suggested, and have provided data, that environmental stimuli may effect tolerance through nonassociative processes (i.e., stress, novelty; cf., [1, 6, 19]). As a control for such nonassociative factors in the present experiment, animals in Groups Expected and Unexpected were treated identically during the pretest tolerance acquisition phase. Furthermore, the design of the present experiment included control animals which received the drug for the first time during testing under either dark, noisy environmental conditions or the light, quiet environmental conditions. The sleeping time of the two control groups did not differ significantly, indicating that there were no differential nonassociative effects of the two environments on the acute effects of pentobarbital in saline-pretreated animals.

Note: There are a number of experimental designs for assessing associative and nonassociative factors in drug effects (cf. Siegel, [19]). The present study used a simple discrimination design. An alternative design is the completely counterbalanced discrimination design (cf. Crowell, Hinson and Siegel, [3]) and it is the case that this design provides a more complete assessment of the potential nonassociative effects of environmental stimuli on drug responsitivity than the simple discrimination design. However, the present study also included two saline control conditions to assess potential nonassociative effects of the different test environments on the acute effects of the drug.

EXPERIMENT 1B

According to the conditioning theory, tolerance to pentobarbital sedation results from the development of a conditional drug-opposite response. Although the exact nature of the conditional drug-opposite response involved in tolerance to pentobarbital sedation cannot be specified, at a general level, it should be manifest as behavioral excitation. Evidence for conditional behavioral excitation was sought in the present experiment in a placebo test.

Conditional behavioral excitability elicited in pentobarbital-tolerant rats expecting pentobarbital might be expected to interact with the behavioral activating effects of cocaine, and to produce potentiated behavioral responses. Experiment 1B was also designed to evaluate whether pentobarbital expectation might potentiate behavioral stimulation by cocaine.

METHOD

Subjects, Drugs and Apparatus

The subjects were the same rats used in Experiment 1A. Details of housing, apparatus, and barbiturate and saline injections were as described in Experiment 1A. Cocaine hydrochloride was dissolved in physiological saline and injected IP at a dose of 60 mg/kg and at a volume of 1 ml/100 g.

Design and Procedure

Following the test session of Experiment 1A, animals were returned to their respective pretest injection schedule for six more injections. Animals in Group Expected and Unexpected received three pentobarbital (45 mg/kg) and three saline injections, one injection every other day, in the drug-injection and saline-injection environments, respectively, described in Experiment 1A. Control animals received six saline injections, three in each of the two injection environments on the alternating schedule. Following these six injections, all animals received a single test session involving the administration of physiological saline. A random half of the drug-experienced and control animals received this test session in the usual pentobarbital-injection environment (Group Expected and Control, respectively). The remaining drug-experienced and control animals received the test session under the usual saline-injection conditions (Groups Unexpected and Control, respectively). This placebo test session was given in a manner identical to that for the tolerance test session of Experiment 1A except that saline was injected instead of pentobarbital: Animals were transported to their designated test environment and placed in the observation boxes. Five minutes after transport, each animal was injected with saline. Animals remained in the boxes for 30 min following injection, after which time they were returned to the animal colony room. Each rat's behavior was videotaped through the test session for subsequent analysis.

Following the placebo test session, all animals were again returned to their pretest injection routine for six additional

injections as previously described. Following these six injections, all animals received a single test session involving the administration of 60 mg/kg of cocaine. A random half of the drug-experienced and control animals received this cocaine test session in the usual pentobarbital-injection environment (Groups Expected and Control, respectively), and the remaining drug-experienced and control animals received the test in the usual saline-injection environment (Groups Unexpected and Control, respectively). This cocaine test session was conducted in a manner identical to that for the placebo test session except that cocaine, instead of saline, was injected.

Behavioral Ratings

For both the placebo and cocaine tests, a single observer blind as to each subject's condition scored the video tapes.

Placebo Test

According to the conditioning theory of tolerance, tolerance to pentobarbital sedation results from a drug-opposite response that may be generally characterized as involving behavioral excitation. Thus, during the placebo test session, behavior was scored using a rating system designed to reflect increasing levels of behavioral excitability. This system was adapted from scales typically employed to rate barbiturate withdrawl behavior (cf., [8], p. 163) and was as follows: (a) asleep or motionless, (b) normal active behaviors, (c) rapid locomotion interrupted by periods of motionlessness, (d) flinching, jerky or jumpy behavior, and (e) convulsions.

Cocaine Test

A scale developed by Ellinwood and Balster [4] to rate the behavioral effects of amphetamine was adapted to rate behavior during the cocaine test. The scale, designed to reflect progressively more intense forms of cocaine-induced behavior, was as follows: (a) Normal, inplace or active behavior, (b) Patterned locomotor activity (e.g., animal continuously walking or running around the observation box in one direction), (c) Stereotyped head and/or limb movements without locomotion, and (d) Dystonic postures usually followed by myoclonic seizures.

During both the placebo and cocaine tests, each rat was assigned the highest-rated behavior achieved during the session.

RESULTS AND DISCUSSION

Placebo Test

During the placebo test, most animals exhibited normal active behaviors (e.g., rearing, grooming, exploratory sniffing). A total of five animals exhibited some instances of "hyperexcitable" behavior (categories "c" or "d"): One animal in each of the two control groups, one animal in Group Unexpected, and two animals in Group Expected. There was no significant difference obtained in any comparison of groups in the placebo test; thus, no direct evidence of conditional responses opposite to pentobarbital sedation was obtained.

Cocaine Test

Since all animals received the high (60 mg/kg) dose of cocaine during the cocaine test session, it was expected that all animals would exhibit some degree of cocaine-induced behavior. Ten of the twelve control animals exhibited either level (b) or level (c) cocaine-induced behavior, which may be taken to represent the level of stimulation that would normally be produced by this dose of cocaine.

The scale used to rate behavior during the cocaine challenge test was designed such that all levels of cocaine-induced behavior less intense than that finally exhibited by each animal also occurred. Typically, animals which exhibited the most-intense forms of cocaine-induced behavior spent less time engaged in the less-intense forms. Consequently, a single measure of each animal's behavior was recorded reflecting the most intense level of cocaine-induced behavior exhibited by the animal in the test session. The number of animals exhibiting each of the progressively more intense forms of cocaine-induced behavior at some time during the test session was as follows for Groups Expected (n=12), Unexpected (n=10) and Control (n=12), respectively: Category *d*, 9, 0, and 2; Category *c*, 12, 2, and 6; Category *b*, 12, 7, and 10. For purposes of statistical analysis, only the number of animals in the different groups which exhibited level *d* behavior was considered.

The number of animals exhibiting category *d* cocaine-induced behaviors was 9 of 12, 0 of 10, and 2 of 12 for Groups Expected, Unexpected, and Control, respectively. An overall chi-square analysis of these data indicated a significant difference among the groups, ($\chi^2=15.96$, $p<0.001$), and subsequent pairwise chi-squares revealed that more animals in Group Expected evidenced level (d) behavior than in either of Groups Unexpected or Control (both χ^2's>8.22, $p<0.005$). There was no significant difference in the number of animals exhibiting level (d) behavior between Groups Unexpected and Control. Of the nine rats in Group Expected that exhibited level (d) behavior, six actually evidenced myoclonic seizures, and three of these died. The two control animals obtaining level (d) behavior during testing both exhibited myoclonic seizures, but did not die. No animal in Group Unexpected evidenced seizures.

The results of the cocaine test demonstrate increased behavioral effects of cocaine in animals expecting pentobarbital. This increased sensitivity to cocaine was not due simply to repeated pentobarbital exposure since animals with the identical pharmacological history but not expecting pentobarbital in the test displayed the "usual" level of cocaine-induced behavior, i.e., the same level as control animals. Furthermore, it is unlikely that the difference in cocaine reactivity between Groups Expected and Unexpected was due to unconditional aspects of the two injection environments since there was no significant difference in cocaine reactivity of saline-pretreated animals tested in the two environments (see *Note*, bottom, p. 663). These results demonstrate that drug expectation based upon one drug (pentobarbital) can augment responsiveness to another drug (cocaine). Thus, the prediction of conditional cross-potentiation was confirmed.

GENERAL DISCUSSION

The results of Experiment 1A demonstrated that drug expectation contributed to tolerance to the hypnotic effects of pentobarbital. This is one of the few demonstrations of Pavlovian control of tolerance to the effects of a sedative-hypnotic on general behavioral arousal [13]. This adds to the

evidence that conditional control of tolerance is demonstrable among the diversity of response systems in which tolerance occurs [18].

Experiment 1B assessed responsiveness to cocaine administered when pentobarbital-experienced animals were either expecting or not expecting pentobarbital. The results demonstrated that rats administered cocaine when expecting pentobarbital exhibited more behavioral stimulation than rats administered cocaine when not expecting pentobarbital. There are other demonstrations of cross-potentiation between drug effects (e.g., [9]), however, the conditional occurrence of cross-potentiation in Experiment 1B is uniquely predicted by Pavlovian theory. Thus, the results of Experiment 1B establish a new phenomenon, conditional cross-potentiation, based on drug expectancy.

According to Pavlovian theory, the conditional cross-potentiation observed in Experiment 1B resulted because stimuli associated with the hypnotic effects of pentobarbital evoked a drug-opposite response which combined with the stimulant effects of cocaine. However, an attempt to produce an observable pentobarbital-opposite response during the placebo test of Experiment 1B failed. In contrast, there have been several direct demonstrations of placebo-elicited drug-opposite CRs with sedative-hypnotics. However, successful demonstrations have involved only thermic effects [3,12]. Thus, it seems likely that the inability to directly detect pentobarbital-opposite CRs in the present experiment was due to the nature of the response system under investigation. There may be an inertia in general behavioral arousal systems which can best be overcome by the addition of a challenge stimulus. Indeed, some type of challenge stimulation is commonly used to reveal the state of latent excitability engendered by chronic exposure to sedative-hypnotics [8]. For example, the literature on physical dependence on sedative-hypnotics is replete with examples of the use of challenge stimuli to provoke withdrawl reactions (e.g., electroconvulsive shock, footshock, the open field, convulsant drugs; [8,14]). In Experiment 1B, cocaine, a psychomotor stimulant, functioned as a challenge stimulus, which revealed a conditional state of excitability in animals expecting pentobarbital which was not observed in the placebo test.

The outcomes of this study have some potentially important clinical implications. It has been suggested [7, 11, 17] that the conditional elicitation of drug-opposite states provides a mechanism for the occurrence of the phenomena of craving and relapse. In fact, the clinical literature contains numerous references to the role of drug-related stimuli in contributing to craving and relapse [17]. Another observation in the clinical literature is that the occurrence of psychological stress is a frequent precipitator of craving and relapse. The present data show that a cocaine challenge revealed a conditional state of excitation engendered by the expectation of pentobarbital which was not detected in the absence of the cocaine (i.e., the placebo test). If the conditional drug-opposite response is accepted as a mechanism for craving, then these data suggest that drug opposite responses and attendant craving may be unmasked by the application of an external stressor. The speculative nature of this analogy is obvious. Although a theoretical relationship between the evocation of conditional drug-opposite responses and drug self-administration can be plausibly argued, substantial experimental support for the relationship is lacking. Additionally, the use of a cocaine challenge test may not adequately represent the actions of psychological stressors. Much more empirical work will be required to turn this speculative analogy into a model for important clinical aspects of relapse. Nonetheless, the principles of Pavlovian conditioning as applied to drugs provide a promising basis for explorations into the mechanisms of craving and relapse.

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