Pharmacology Biochemistry & Behavior, Vol. 25, pp. 35–40, 1986. © Ankho International Inc. Printed in the U.S.A. 0091-3057/86 $3.00 + .00

Sodium Pentobarbital-Induced Cross-Tolerance to Ethanol is Learned in the Rat

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Received 22 May 1982

WENGER, J. R., P. M. McEVOY AND S. C. WOODS. *Sodium pentobarbital-induced cross-tolerance to ethanol is learned in the rat.* PHARMACOL BIOCHEM BEHAV **25**(1) 35–40, 1986.—Initially, rats were trained to walk on a treadmill to avoid footshock. Subsequently, rats given additional practice while pentobarbital-intoxicated became cross-tolerant to ethanol. However, rats given equivalent doses of pentobarbital after practice did not become cross-tolerant, nor did saline-vehicle controls. These results challenge the theories of cross-tolerance which are based exclusively upon cellular adaptations to pharmacological stimulation of drug-responsive neurons. That all of the cross-tolerance measured was attributable to the intoxicated practice suggests that this observed cross-tolerance was mediated by some form of learning.

Behavioral tolerance Classical conditioning Cross-tolerance Ethanol Instrumental learning Learning Sodium pentobarbital Tolerance Two-factor theory of learned tolerance Two-factor theory of learned cross-tolerance

CROSS-TOLERANCE between two drugs is the phenomenon wherein an organism has a decreased response to one drug as a consequence of previous treatment(s) with the other drug [7]. Cellular theories of tolerance and cross-tolerance postulate cellular adaptations to chronic pharmacological stimulation of drug-responsive neurons as the mechanisms of tolerance and cross-tolerance [14]. On a more molar level, learning theories have been proposed to explain the development of tolerance to some of the physiological effects of ethanol [8, 10, 15] and pentobarbital [1] and to some of the behavioral effects of ethanol [2, 3, 5, 22–25].

Learning theories of tolerance may also be able to explain cross-tolerance between depressant drugs. However, other than our original preliminary report of learned cross-tolerance [21], there has been only one other report supporting this hypothesis [1]. That study reported that classical conditioning mediates cross-tolerance to the hypothermic effect of pentobarbital and ethanol. The present report details evidence that learning mediates the development of cross-tolerance to a behavioral effect common to both pentobarbital and ethanol.

METHOD

Animals

The subjects were 30 experimentally naive male Long-Evans rats approximately 90 days old. They were housed individually in standard galvanized iron hanging cages in a vivarium illuminated from 0800 to 2000 hours. The animals were given free access to food (Purina rat chow) and water throughout the experiment. Each day the animals were weighed in the vivarium, and then placed into stainless steel holding cages. They were then transported on a laboratory cart to the hallway outside of the room which contained the apparatus.

Apparatus

The apparatus was an automated treadmill which forces rats to walk upon a proverbial "straight line" (operationally defined as the treadmill belt) in order to avoid footshock from an electrified grid floor [6,22]. The treadmill chamber was 38 cm long by 32 cm wide by 20.7 cm high. The treadmill belt was 6.35 cm wide and moved 8.3 cm/sec lengthwise through the middle of, and horizontally flush with, the grid floor of the chamber. The floor was electrified such that it would deliver a constant current 0.95 milliampere sinusoidal unscrambled shock to the foot of a rat. Any contact by the rat with the floor was electronically detected and accumulated for each trial in tenths of a sec. The apparatus automatically executed the following cycle: a 60-sec data-acquisition trial during which the belt was moving, followed by a 30-sec rest-period wherein the belt no longer moved but the floor remained electrified. Three successive cycles composed a standard four-minute treadmill session.

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Treadmill Shock-Avoidance Pre-Training

Undrugged animals were trained to walk the treadmill by giving them three daily practice trials, five days per week, until the animals consistently received no more than one sec of footshock per 60-sec trial. Initially, clear Plexiglas training-walls were placed alongside both sides of the treadmill belt. Their purpose was to restrict the ability of the animals to move laterally while they were beginning to learn to walk upon the treadmill belt. Later, these walls were gradually moved away from the belt so that the animals could learn to remain on the belt in order to avoid the electrified grid floor. Eventually the walls were removed completely. This training procedure was adjusted according to the learning rate of each rat.

All of the animals initially received one practice session per day until each animal satisfied the criterion of receiving less than one second of shock per trial for three consecutive weekday sessions. As soon as they met this criterion, the quicker learning animals were withdrawn from training until the slower learning animals also learned the task. The animals required one to three weeks to learn the task. Then all of the animals were given additional practice until they all once again satisfied the training criterion. This took about four weeks in all.

The animals were rank-ordered with respect to their quickness (the number of days each animal required) to learn the task. This rank-ordering was used in combination with random assignment to balance the experimental groups. This was done by taking the three quickest learners, and randomly assigning one of them to one of the three experimental groups, and then randomly assigning the remaining two animals to the remaining two groups. This process was then repeated with the next three quickest learners, etc. Thus, the experimental groups were not matched with regard to total pre-training, but were matched with regard to, the presumably more important factor, quickness to learn to walk the treadmill.

Tolerance Induction and Measurement of Cross-Tolerance

The experimental procedure had three phases: (1) determination of the pentobarbital-dose-effect relationship; (2) pentobarbital-tolerance-induction treatments; and (3) testing for cross-tolerance to ethanol. Thirty treadmill-trained but drug-naive rats were first assigned as described above to one of the three equally sized treatment groups. All of the animals were then used to determine the drug-naive pentobarbital-dose-effect relationship for the treadmill-task. In this determination, each animal was tested twice, one week apart and at a different dose of pentobarbital. The experimental groups were approximately balanced with regard to the amount of pentobarbital which they received during the determination of the dose-effect relationship. The three groups, which are described further below, received 15.0±0.5 (mean±s.e.m.), 15.0±0.5, and 14.1±0.4 mg/kg respectively on the first day, and 13.0±0.9, 13.2±0.9, and 12.8±0.9 mg/kg respectively on the second day.

Three days after the determination of the pentobarbital-dose-effect relationship, a nine-day sequence of pentobarbital-tolerance-induction treatments was begun. One group, designated the Intoxicated Practice Group, was given daily a standard three-consecutive-trial treadmill session 15 min after an intraperitoneal (IP) injection of sodium pentobarbital. These animals were brought into the experimental room, injected with pentobarbital, and then run on the treadmill fifteen minutes later. The animals were not handled within a treadmill-session. Each of these animals was removed from the experimental room immediately upon completion of its tolerance-training session. Thus, each of these animals experienced pentobarbital-induced intoxication in the experimental room a total of nineteen minutes.

A second group of animals, designated the Pentobarbital-Exposure Group, was given first a standard treadmill session while unintoxicated, and then, 15 min later, injected with the equivalent dose of pentobarbital received by the rats in the first group. These animals were first brought into the room and run on the treadmill. Immediately upon completion of their treadmill sessison, they were returned to their holding cages on the laboratory cart outside of the experimental room. Then, 15 min later, they were injected with pentobarbital and returned to their home cages. Thus, the second group had equal exposure to the pentobarbital, treadmill, and experimental room, but did not practice on the treadmill while intoxicated, and did not experience pentobarbital-induced intoxication in the experimental room.

The final group, designated the Vehicle-Control Group, was injected daily with the saline vehicle (0.9% w/v) 15 min prior to a standard treadmill-session. These animals were treated exactly like those in the Intoxicated Practice Group except that their injections contained no pentobarbital. Thus, all three groups received equal practice on the treadmill and equal exposure to the stimulus properties of the apparatus and of the experimental room.

A series of increasing doses of pentobarbital was used because we reasoned that if tolerance to pentobarbital were to occur as a result of learning then pentobarbital-tolerance would be acquired optimally if the difficulty of the task increased gradually. Hence, the series of doses was 12, 13, 14, 15, 16, 17, 18, 18, and 18 mg/kg of pentobarbital per day. All of the animals were given one preliminary unintoxicated trial on the treadmill each day to verify that their baseline performance had not changed. To accomplish this, each animal was removed from his cage, brought into the experimental room, given one run on the treadmill, and immediately removed from the room. Thus, the total time spent in the room and on the treadmill was the same for all of the animals.

Following the induction of tolerance to pentobarbital, the animals were given two non-drug days without practice on the treadmill to allow the pentobarbital to be cleared from their bodies. On the third day, they were tested for cross-tolerance to ethanol, 2.8 g/kg (15% w/v in saline 0.9% w/v). A one-hour interval between the injection of ethanol and the testing for cross-tolerance was chosen to ensure that absorption of ethanol would be complete and to make the results directly comparable to our previous studies of tolerance to ethanol [22–24].

There was no *a priori* method to determine the dose of ethanol which would be optimal for testing for cross-tolerance. Therefore, we referred to an ethanol-dose-effect curve from a previous experiment [24]. On the basis of these data, two rats from each group were randomly selected and injected with 2.0 g/kg of ethanol. However, all of these rats were relatively unimpaired by this dose. We therefore randomly selected two additional rats from the Vehicle-Control Group and injected them with ethanol 3.0 g/kg. This dose resulted in nearly maximal impairment. We then tested two more of these animals with ethanol 2.8 g/kg, and found them to be severely but not totally incapacitated by this dose. Therefore all of the remaining animals were injected with

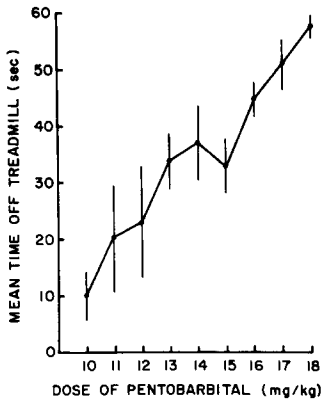

FIG. 1. Dose-effect relationship between doses of pentobarbital administered intraperitoneally to thirty treadmill-trained but drug-naive rats and their performance on the treadmill fifteen minutes later. The values shown are group means±s.e.m. and are based upon three to eleven animals per dose.

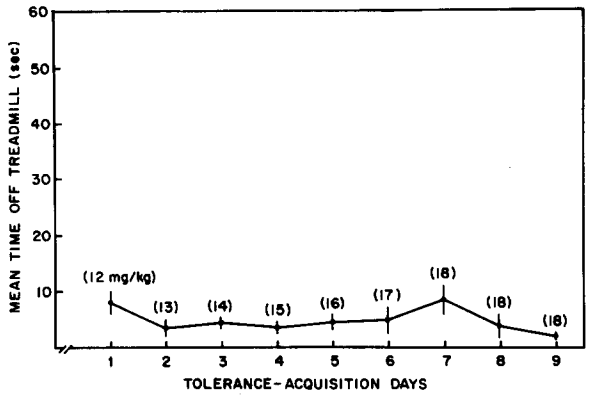

FIG. 2. The acquisition of tolerance to pentobarbital by the Intoxicated Practice Group. This group received pentobarbital-intoxicated practice daily as indicated. The values shown are means±s.e.m. The daily dose of pentobarbital administered is indicated above each data point.

ethanol 2.8 g/kg and tested on the treadmill for cross-tolerance. One rat in the Vehicle-Control Group died reducing the size of this group to five.

RESULTS

A repeated measures analysis of variance indicated that the performance of the daily unintoxicated pre-run trial did not change as the experiment progressed, $F(9,27)=0.54$, N.S., nor was the performance affected by the experimental treatments, $F(2,27)=0.99$, N.S., nor was it affected by the interaction of the experimental treatment with days of the experiment, $F(18,243)=0.005$, N.S.

Figure 1 depicts the pentobarbital-dose-effect curve. It can be seen that an 18 mg/kg dose of pentobarbital almost totally disrupted the performance of drug-naive rats on the treadmill-task.

Figure 2 depicts the development of tolerance to pentobarbital for the pentobarbital-intoxicated practice group. The acquisition of tolerance was manifested as a relatively constant treadmill-error score despite the daily increasing doses of pentobarbital. By the ninth day, rats receiving 18 mg/kg of pentobarbital averaged 1.38±0.41 sec of error. This can be compared to the response of drug-naive rats (cf. Fig. 1) which spent an average of 57.4±1.6 sec off of the treadmill when administered this dose of pentobarbital.

Figure 3 summarizes the results of the test for cross-tolerance. Only the first of the three trials of the cross-tolerance test-session was analyzed in order to exclude the possibility of intrasessional practice effects [9]. The obtained values were: Intoxicated Practice Group, 25.6±5.4 sec (mean±s.e.m.), n=8; Pentobarbital-Exposure Group, 51.9±1.8 sec, n=8; and Vehicle-Control Group, 46.1±6.7 sec, n=5. Planned paired comparisons using the Cochran-Cox approximate t-test for unequal sample sizes and variances [4] revealed that the animals in the Intoxicated Practice Group spent significantly less time off the belt than the animals in the Pentobarbital-Exposure Group ($t(12)=4.62$, $p<0.005$). The Pentobarbital-Exposure Group and the Vehicle-Control Group were not reliably different from each other ($t(11)=0.84$, $p>0.45$). Furthermore, their responses

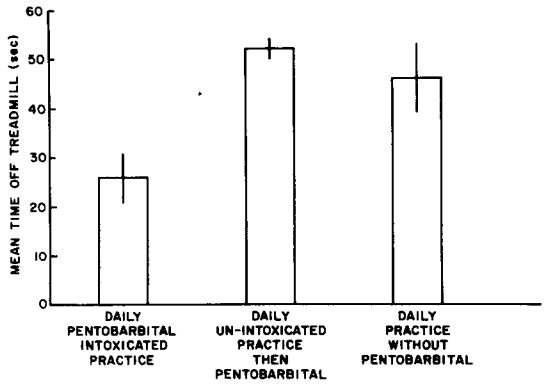

FIG. 3. Cross-tolerance to ethanol (2.8 g/kg, IP) as a function of previous history of pentobarbital intoxication and practice on the treadmill. The abscissa indicates the experimental treatments which were administered on the previous nine days. The adjusted sizes of the three groups from left to right respectively were 8, 8, and 5.

were similar to what would be predicted of drug-naive rats receiving 2.8 g/kg of ethanol.

DISCUSSION

The most important finding of this experiment was that the pentobarbital-intoxicated-practice animals became behaviorally cross-tolerant to ethanol whereas the pentobarbital-exposure controls did not. All of the statistically reliable pentobarbital-induced cross-tolerance to ethanol was attributable to some aspect of the effects of behavioral practice while intoxicated with pentobarbital, thereby suggesting that some form of learning was involved. Moreover, there was no detectable component of cross-tolerance that could be attributed to chronic pentobarbital exposure *per se* since the Pentobarbital-Exposure Group, whose history of pharmacological stimulation was identical with that of the Intoxicated Practice Group, performed no better than the Vehicle-Control Group which had never been given pentobarbital. This finding is not easily reconcilable with theories of tolerance and cross-tolerance based upon

either cellular adaptations resulting from pharmacological stimulation *per se*, or upon drug-dispositional mechanisms. However, the present data are consistent with the hypothesis that learning processes mediate, at least in part, the development of tolerance to, and cross-tolerance between, the performance-impairing effects of sedative-hypnotic drugs.

Would tolerance to pentobarbital or cross-tolerance to ethanol eventually result from passive drug exposure if only the passive pentobarbital-exposure period were sufficiently long? It has been reported that chronic exposure to ethanol is sufficient to induce ethanol tolerance provided that the ethanol-exposure period is sufficiently long [11,12]. In these experiments, on three out of every four days, the Ethanol-Exposure Group received ethanol after their daily practice session. However, on every fourth day, in order to monitor the rate of the development of tolerance presumed induced by the passive exposure to ethanol (i.e., non-learned tolerance), these animals were tested behaviorally for tolerance. This raised the possibility that the act of measuring tolerance behaviorally every four days might actually have been causing tolerance to develop through the mechanism of learning to cope with this impairment of behavior during this tolerance testing.

Subsequently, a direct test of this hypothesis found that all of the behavioral tolerance to ethanol which developed in the intermittently tested animals was due to the intoxicated practice which these animals had received [24]. This strongly suggested that passive chronic exposure to ethanol, at least for periods of up to twenty-two days, does not, by itself, induce tolerance to ethanol. Moreover, there are at present no properly controlled experiments in the literature which demonstrate behavioral tolerance to ethanol which can not be explained by the principles of learning [25]. Similarly, there are no properly controlled experiments which suggest that cross-tolerance to ethanol can result from passive exposure to the induction-drug. Until such evidence appears, it is theoretically more parsimonious to state simply that cross-tolerance to ethanol results from pentobarbital-intoxicated practice but not from passive exposure to pentobarbital.

The present cross-tolerance results suggest that behavior-dependent learning processes are involved. For example, through learning, drug-compensatory CNS mechanisms may become activated in the combined presence of the drugs and the cross-tolerance-testing situation, thereby countering the drug effects, and thus mediating the phenomenon of cross-tolerance. Just as both of the two major types of learning have been proposed as explanations of tolerance to the effects of a variety of drugs [8, 10, 15, 16–20, 22–26], the present cross-tolerance results are also interpretable as being due to either the principles of instrumental learning or classical conditioning.

For example, the instrumental learning model of drug tolerance [22] can be further generalized as indicated below to explain the present cross-tolerance results. According to this generalized instrumental learning model of tolerance and cross-tolerance, both tolerance and cross-tolerance result from the instrumental learning of both task-specific and task-non-specific behaviors. These behaviors are emitted originally because they help to reduce the drug-induced impairment of the performance of the specific task. In the context of the treadmill-task, examples of task-specific behaviors might include walking at a constant rate, walking carefully so as to keep the paws from touching the shock grid, lowering of the center-of-mass in order to improve balance, etc. Examples of task non-specific behaviors might include generalized increases of attention, arousal, goal-directedness, and, perhaps, decreases of emotionality, etc. According to this generalized instrumental learning model, these specific and non-specific behaviors while intoxicated constitute behavioral tolerance. Whatever the exact nature of the drug-compensatory behaviors, they would tend to be emitted subsequently in response to the exteroceptive stimuli associated with the apparatus (the task), the interoceptive stimuli associated with the functional demands of performing the task while intoxicated, and the interoceptive stimuli associated with being intoxicated *per se*. These drug-associated, task-associated, and task-plus-drug-associated stimuli subsequently function as discriminative stimuli to inform the animal of the behavioral demands of being intoxicated while performing the task. In the tolerance-test these stimuli effectively control the behaviors which constitute tolerance.

However, in a test of cross-tolerance, the tolerance-induction drug is not present, but is instead replaced with the cross-tolerance-test drug. Notably, the stimulus properties of the two drugs will be somewhat different. For this reason, the degree of cross-tolerance which is expressed here will generally be less than the degree of tolerance which is expressed during a test of tolerance. According to this model, the exact degree of cross-tolerance which is expressed depends, in part, upon the degree of stimulus generalization between the stimulus properties of the two drugs.

Another reason to expect that expressed cross-tolerance will in general be less than expressed tolerance is that in general the effects of the cross-tolerance test-drug will be somewhat different than those of the tolerance-inducing drug. Different drug effects would lead to different impairments of behavior. Consequently, different coping behaviors would be required in order to compensate.

This generalized instrumental learning model of tolerance and cross-tolerance also can explain the previously unexplained findings of LeBlanc *et al.* [12] that ethanol tolerance was not task-specific in that it transferred between behavioral tasks. In particular, these investigators found that rats trained to perform the treadmill-task while they were ethanol-intoxicated were also tolerant to the disruptive effects of ethanol upon the performance of a circular maze task. These animals had previously learned to perform this maze task while they were not intoxicated. Moreover, this task-non-specificity of tolerance was symmetrical in that the tolerance transferred equally well in both directions, i.e., animals tolerant on either task were also tolerant when they were tested on the other task.

These results would be predicted by the generalized instrumental learning model of tolerance and cross-tolerance described above. One would predict that, to the extent that there were drug-compensatory behaviors common to the two behavioral tolerance-measurement tasks, tolerance would generalize across tasks. It should be clear that one common denominator between *walking while intoxicated* on a treadmill, and *walking while intoxicated* around a circular maze is *walking while intoxicated*. Furthermore, there may be other behaviors in common to the two behavioral measures of tolerance.

The present cross-tolerance results are also explainable by mechanisms based upon classical conditioning [1]. According to the classical conditioning model of drug tolerance, environmental stimuli associated with the drug administration and experience of intoxication acquire the capability to

elicit, through the process of classical conditioning, compensatory responses [8]. The stimuli associated with this environment become conditioned stimuli for the elicitation of the drug-compensatory responses. Thus, animals which experienced a sufficient amount of pentobarbital-induced intoxication in a particular environment would eventually compensate for the intoxication thereby becoming pentobarbital-tolerant in this stimulus environment. However, they would not necessarily express this tolerance in other environments with dissimilar stimuli.

According to this interpretation, cross-tolerance between the effects of two drugs may be regarded as being due to the expression of tolerance to the first drug while being intoxicated with the second drug. The expression of this tolerance to the first drug as cross-tolerance to the second drug is controlled by the stimuli to which the tolerance are conditioned [1]. Moreover, as discussed above in the generalized instrumental learning model, the effectiveness of the expressed cross-tolerance at reducing the drug-induced impairment of performance also depends upon the similarity of the two sets of drug effects as assessed operationally by the particular behavioral assay of cross-tolerance.

In the present experiment, both of the pentobarbital-treated groups received equal practice on the treadmill, equal exposure to pentobarbital, equal time in the experimental room, but did not receive equal exposure to the stimuli associated with the experimental room while the animals experienced intoxication. Thus, according to the classical conditioning model of cross-tolerance, only the pentobarbital-intoxicated practice group should have become tolerant to the pentobarbital. Although this may have happened, the present experiment did not test this prediction. However, this prediction was confirmed by another experiment (Wenger *et al.*, in preparation). Similarly, only the pentobarbital-intoxicated-practice group should have become cross-tolerant to ethanol.

Perhaps the Pentobarbital-Exposure Group would have expressed cross-tolerance to ethanol if they had been tested differently. For example, the animals in this group may have become conditioned to, and tolerant to, the intoxicating effects of pentobarbital in their home cages. This conditioned tolerance to pentobarbital might have been expressed as cross-tolerance to ethanol if these animals had been injected with ethanol and kept in their home cages until just before being tested for cross-tolerance to ethanol.

Additionally, the principles of classical conditioning may be able to explain the present results as follows: During the tolerance-induction period, the animals in the Intoxicated Practice Group made more errors, received more footshock, and may have consequently learned to fear the treadmill apparatus. Later, during the test for cross-tolerance, the increased arousal associated with this conditioned fear may have partially physiologically antagonized the depressant effect of the ethanol, and thereby mediated the observed cross-tolerance. The present data support this interpretation. That this interpretation is true may be important theoretically. This would constitute the first reported instance of cross-tolerance classically conditioned, not to stimuli associated with intoxication *per se*, i.e., to the room containing the treadmill, but to the stimuli associated with either the treadmill itself (thereby suggesting very specific stimulus discrimination), or with the behavior of walking on the treadmill while intoxicated.

It might be argued that non-associative factors could plausibly account for the present cross-tolerance results. For example, the differential activity of the two pentobarbital-treated groups may have resulted in different brain concentrations of pentobarbital, and therefore differences in pentobarbital effect, thereby inducing different levels of tolerance and cross-tolerance. Specifically, the greater physical activity of the Intoxicated Practice Group may have resulted in greater brain-concentrations of pentobarbital and thereby induced greater cross-tolerance to ethanol than in the Pentobarbital-Exposure Group. However, this non-associative explanation can not explain why there was no detectable cross-tolerance in the Pentobarbital-Exposure Group.

Comparison of Figs. 1 and 2 shows that the procedure for determining the pentobarbital-dose-effect relationship may have produced detectable tolerance to pentobarbital on the first day of the pentobarbital-tolerance-induction procedure; i.e., rats receiving pentobarbital 12 mg/kg. However, an alternative interpretation is that these animals had become more resistant to the behaviorally disruptive effects of the pentobarbital because of the additional practice which they had received during the determination of the dose-effect relationship. In either case, the three experimental groups were closely balanced with respect to the amount of pentobarbital which they received during the determination of the dose-effect relationship. Thus, no differential effects of practice, neither intoxicated nor unintoxicated, would have been expected to carry over into the cross-tolerance-inducing procedure.

In summary, the present data indicate that pentobarbital-intoxicated practice, but not pentobarbital-intoxication without practice, induces cross-tolerance to ethanol. These data extend earlier observations that ethanol-intoxicated practice, but not ethanol-intoxication without practice, induces tolerance to ethanol. Collectively, these observations support the hypothesis that some form of learning mediates, at least in part, the development of tolerance to, and cross-tolerance between, the behavioral effects of depressant drugs. The present cross-tolerance results could be the result of either instrumental learning processes, or classical conditioning processes, or both. The present data do not uniquely support either explanation. Until such data become available, it seems reasonable to conjecture that the processes of instrumental learning and classical conditioning mediate different aspects of cross-tolerance between sodium pentobarbital and ethanol. More importantly, this two-factor theory of learned tolerance and cross-tolerance may also explain the phenomena of cross-tolerance between other drugs.

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