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BRIEF COMMUNICATION

Barbital-Induced Changes in Sensitivity to the Behavioral Effects of Narcotics[1]

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CARNEY, J. M. AND J. A. ROSECRANS. *Barbital-induced changes in sensitivity to the behavioral effects of narcotics.* PHARMAC. BIOCHEM. BEHAV. 6(5) 589–590, 1977. –Twelve male (Sprague-Dawley) rats were trained to respond under a variable-interval 15 sec schedule of sweetened-milk reinforcement. Rats were tested with doses of morphine and methadone, both before and after the development of tolerance to barbital (100 mg/kg, IP). Barbital-tolerant rats were tolerant to the effects of methadone on VI responding but were not tolerant to the effects of morphine. These data demonstrate that tolerance to some narcotics can develop after chronic exposure to drugs other than those of the same pharmacologic class. Furthermore, this investigation demonstrates the necessity of considering changes in the pharmacokinetics of a narcotic as a possible explanation for the development of tolerance to the behavioral effects of the drug.

Variable-interval schedule Barbital tolerance Morphine Methadone Cross-tolerance

EVIDENCE of cross-tolerance between drugs has been used as one criterion for identifying compounds which possess similar pharmacologic properties [6,10]. For example, morphine-tolerant animals exhibited cross-tolerance to a number of other narcotics but not to drugs of a different pharmacological class [3]. Tolerance can develop as the result of either a change in the sensitivity of the target cell to an agonist (cellular adaptation) or can be the result of a change in the disposition of the compound in the body (dispositional tolerance), or both. Previous studies have demonstrated that daily oral methadone [11], or the chronic administration of pentobarbital or phenobarbital [1,9], can result in the development of tolerance to the antinociceptive and lethal effects of methadone. These changes in sensitivity to methadone were ascribed to, in part, an increase in hepatic N-demethylase activity. In these studies, barbiturate treated rats were tolerant to methadone but not to morphine. In addition, the differential tolerance observed to methadone was consistent with the metabolic model of tolerance, especially since methadone is N-demethylated to a greater extent than is morphine.

The present study was conducted to determine if the daily administration of barbital, a barbiturate which is metabolized to only a limited extent (3–5% of the administered dose; see [7]), would result in a change in sensitivity to the behavioral suppressive effects of methadone or morphine on schedule-controlled responding in rats.

METHOD

The animals used in this study were 12 male Sprague Dawley rats which weighed between 300 and 400 g when allowed free access to food. The animals were part of a larger study on the behavioral and biochemical effects of chronic exposure to barbital [2]. The animals weights were reduced to 80% of their ad lib weights by partial food deprivation. Except for the 1/2 hr period during behavioral testing, the animals had free access to water throughout the day. The rats were trained to respond under a variable-interval 15 sec (VI 15 sec) schedule of sweetened milk presentation. Each daily session lasted for 30 min and animals were run every day (7 days/week). Under the VI 15 sec schedule, an 0.1 ml dipper, filled with sweetened milk, was presented after the first response following a variable time period since the last dipper presentation (average time = 15 sec). The dipper was held up for a period of 5 sec.

Test doses of morphine and methadone were injected (IP) 30 min before the start of each experimental session.

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In addition to morphine and methadone, test doses of barbital, pentobarbital, diphenylhydantoin, and ethanol were also studied during similar sessions (this data is presented in [2]). Rats were made tolerant to barbital (100 mg/kg/day) by the daily administration of the drug for a period of more than 3 months. Rats were retested with the various drugs after tolerance had developed. On the day before testing, saline was substituted for barbital and the test drug was given 30 min before the start of the session on the day following saline substitution (48 hr since the last barbital injection). The rats were divided into two groups of 6 rats. One group was tested with methadone and the other group was tested with morphine. *d,l*-Methadone, morphine SO_4, and Na barbital doses refer to the salt. All drugs were dissolved in sterile 0.9% solution.

RESULTS

The average control rates of responding under the VI 15 sec schedule were 0.49 responses/sec ± 0.06 (SE). Both morphine and methadone produced decreases in VI responding at the doses tested (Fig. 1). Methadone was about twice as potent as morphine in decreasing responding. When rats were retested after the development of tolerance to barbital, the methadone treated group showed a reduced sensitivity to methadone while the morphine treated group showed no change in sensitivity to morphine.

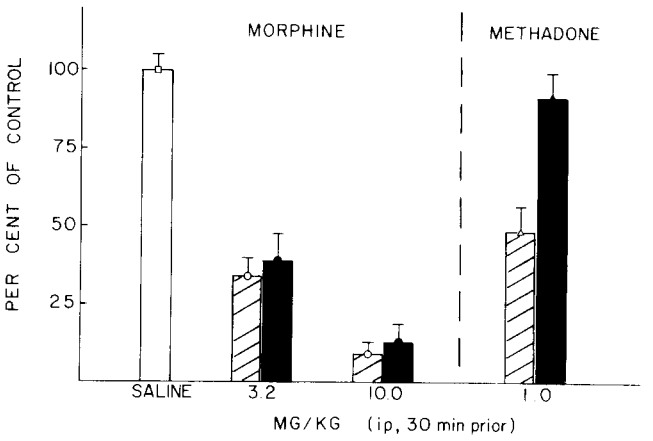

FIG. 1. Effects of morphine and methadone on responding under a variable-interval 15 sec schedule of responding in barbital tolerant (solid bars) and nontolerant (cross-hatched bars) rats. Morphine and *d,l*-methadone were tested in different groups of 6 rats each. Saline values represent the control performance of all 12 rats. Rats were made barbital tolerant by the repeated daily administration of 100 mg/kg barbital (IP). Values represent the mean (± SE) for 6 rats at each dose.

DISCUSSION

The present study demonstrated that the chronic treatment of rats with a barbiturate (barbital) can result in a reduction in the behavioral suppressive effects of methadone with no change in sensitivity to the effects of morphine. Interestingly, a similar reduction in the effects of methadone was observed previously after chronic exposure to either pentobarbital [9] or phenobarbital [1]. Both of these latter barbiturates are not only adequate stimuli for the induction of hepatic microsomal enzymes, but they are also good substrates for hepatic enzymes [4]. Barbital, on the other hand, differs from these two barbiturates in that it can induce hepatic microsocmal enzymes [5] but is a poor substrate for the metabolizing enzymes. Thus, it seems that the reduction of methadone's behavioral suppressive effects was the result of increase in it's metabolism via a hepatic induction of microsomal enzymes by barbital [4].

Previous studies concerning the development of tolerance to the behavioral effects of morphine and methadone have used chronic exposure to narcotics to produce tolerance [3,8]. The present study indicated that tolerance to the effects of methadone on schedule-controlled responding can develop after chronic treatment with a barbiturate (barbital). It is unlikely that this tolerance was due to a change in sensitivity of the CNS to narcotics, since there was no change in sensitivity to morphine. These results point out the need for considering the possible development of metabolic or dispositional tolerance in any study of the development of tolerance to the behavioral effects of drugs that are substrates for hepatic microsomal or other enzymes.

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