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Naloxone-induced aversion to sucrose in morphine-dependent rats

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Two groups of Wistar strain rats, 10 morphine-dependent and 6 normal controls, were given 4% sucrose solution to drink for 15 min followed by intramuscular injection with naloxone (8 mg). Morphine-dependent subjects showed a marked aversion to sweet water in a postconditioning two-bottle preference test. Control subjects preferred the sucrose solution. The results suggest that naloxone-induced taste aversion may provide a useful measure of morphine dependency.

Association of a novel flavor with various types of postingestional stress produces either a reduction in consumption or a complete avoidance of the taste stimulus. Taste aversions have been conditioned to a variety of gustatory stimuli such as saccharin (Garcia, Kimeldorf, & Koelling, 1955), saline (Perry, 1963), and sucrose (Smith & Birkle, 1966). Current literature is replete with reports of substances which reliably produce the bait-shyness phenomenon. Commonly used agents have been lithium chloride, apomorphine, cyclophosphamide, and ionizing radiation. Recently, Parker, Failor and Weidmand (1973) noted that morphine-addicted rats sometimes manifested aversions to solutions inadvertently paired with the onset of withdrawal stress.

Abrupt withdrawal of morphine from an organism which has become dependent upon periodic doses of the drug results in severe physiological disturbances. Commonly observed signs of the abstinence syndrome are inactivity, piloerection, diarrhea, and wet-shake behavior. Their occurrence is usually taken as evidence of drug dependence. However, wide variability in both the severity and number of signs observed in withdrawn animals make the reliable identification of dependent animals a difficult task.

Naloxone, a narcotic antagonist, will rapidly reverse the effects of morphine. In dependent organisms, it will elicit the abstinence syndrome. It has no observable effect in nondependent organisms if no narcotic is present in the system. Goldberg and Schuster (1967) have demonstrated that low doses of nalorphine, another antagonist to morphine, will suppress food reinforced fixed-ratio responding in morphine-dependent monkeys. The present experiment demonstrates that rats which had previously learned to prefer morphine developed profound aversions to sucrose when it was paired with a single injection of naloxone. Nondependent controls which were also injected with naloxone preferred to drink the sucrose solution.

METHOD

Subjects

Subjects were 16 Wistar strain rats which ranged in age from 180 to 200 days old at the start of the experiment. They were housed in standard Hoeltge wire rat cages in an open-air animal shelter at the Caribbean Primate Research Center, Sabana Seca, Puerto Rico. Ten of these subjects had been maintained with ad-lib food and a .3-mg morphine sulfate/ml *tap* water as their only source of liquid for 100 days prior to the start of the experiment. The remaining six subjects had been maintained with ad-lib food and water during this period.

Procedure

The average daily self-administered dose of morphine was determined for each member of the morphine group just prior to the start of the experiment. On the first day of the experiment, all subjects were deprived of food and liquid at 12:00 p.m. At 9:00 a.m. the following day, the morphine subjects were injected intramuscularly with the average amount of morphine which each subject would normally be expected to ingest in a 24-h period. All other subjects were injected with 1 cc of physiological saline. Four hours later, all subjects were presented with a bottle containing 4% sucrose solution for 15 min. All subjects were observed to drink sucrose during this CS presentation period. Subsequently, all subjects were injected intramuscularly with 8 mg naloxone HCl. Following this treatment, liquid and food deprivation were continued for 23 h. A 72-h two bottle preference test between 4% sucrose and water was then initiated. At the end of the first 24 h of preference testing, the bottles on each cage were removed for weighing and refilling. Bottles were replaced in reversed positions from the original 24 h of the test in order to control for side preferences. Each day during the preference test, morphine subjects were injected at 9:00 a.m. with their mean daily dose of morphine while control subjects were injected with 1 cc of physiological saline. Each subject's preference for sucrose was determined by calculating the proportion of the total liquid intake that was sucrose for each of the three 24-h test periods.

RESULTS

The mean sucrose preference scores are shown as a function of test days in Figure 1. An analysis of variance for repeated measures, unweighted-means solution (Winer, 1962), was performed on these data. The groups

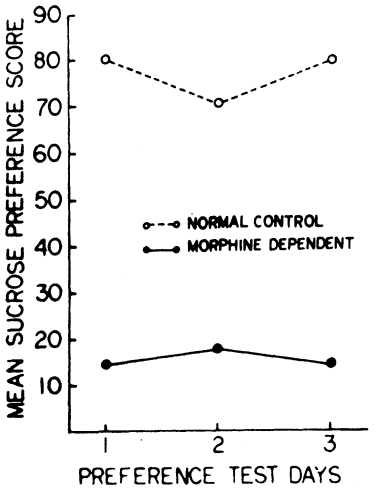

Figure 1. Postconditioning group preferences for 4% sucrose.

effect was significant ($F = 120.94$, $df = 1/10$, $p < .001$). The repeated measures effect and the Groups by Measures interaction were not significant.

DISCUSSION

The results of the analysis indicate that a profound aversion to sucrose was conditioned using a single pairing of naloxone and 4% sucrose. Normal controls, i.e., subjects with no dependence on the drug were unaffected by the injection of naloxone. The observation that withdrawal stress can serve as a motivating stimulus to condition a taste aversion has been reported by Parker et al. (1973). Although they did not investigate the effect systematically, it was suggested that the procedure might offer a simple technique for screening drugs.

The present experiment was performed for the purpose of identifying morphine dependent rats. Previously it was demonstrated that rats forced to drink weak morphinized solutions for 84 days became dependent upon the drug to the extent that they chose to consume more of the morphine solution than water when both were made concurrently available (Ternes, in press). However, preference is not a sufficient measure of drug dependence, since it is at least conceivable that an animal may become dependent on a low dose of morphine and still consume a greater proportion of water than morphine solution. Neither is the occurrence of abstinence syndrome a reliable measure of dependence, since withdrawal stress is a highly variable phenomenon which is difficult to quantify. Observed behaviors of the morphine rats following the administration of naloxone ranged from inactivity and piloerection to diarrhea and shivering. Many of the normal controls were also observed to be diarrhetic, inactive, and have piloerection following naloxone injection. However, all of the morphine animals developed strong aversions to sucrose, while all of the control subjects consumed large quantities of sucrose throughout the preference test. These results suggest that naloxone induced taste aversion could be used as a technique for identifying morphine dependency in rats.

Parker et al. (1973) demonstrated that preferences for sucrose-octa-acetate were increased when its consumption was followed by relief from withdrawal stress. The present study demonstrated the converse, that an aversion to sucrose was produced when it was paired with the onset of withdrawal stress.

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