Establishment of morphine preference in the rat*

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Three groups of rats were placed on sucrose morphine and milled rat food for 25 days. Morphine HCl content was .5 mg/ml for all three groups. Sucrose concentrations were 2.5%, 5%, and 10%. In a subsequent choice test, all three groups selected their respective sucrose morphine over tap water. In an additional choice test given to the 10% group, the rats selected the sucrose morphine over the vehicle. We report on a highly effective oral method of inducing morphine preference.

There is a general agreement that drug research with infrahuman organisms can be of potential value for understanding the mechanisms of dependence in man. Commonly employed procedures for studies of dependence in animals involve chronic administration of drugs via intraperitoneal, subcutaneous, and intravenous routes. Although the oral method of drug administration is the simplest, most economical, and used most frequently in human medications, this procedure has not been widely employed in animal research (Schuster & Thompson, 1969). In the case of opiates, a few investigators (e.g., Thompson & Ostlund, 1965; Stolerman & Kumar, 1970), employing the oral method of morphine administration, have successfully produced drug dependence in the rat. However, since morphine is a bitter substance, rats must be forced to drink morphine solutions. We now report data that show that rats ingest high quantities of morphine when the drug is presented in a sucrose medium and that they prefer sucrose morphine to sucrose alone.

METHOD

The Ss were 11 male Holtzman Sprague-Dawley rats, 170-190 days old at the start of the experiment. Each rat was individually housed in a standard laboratory cage with free access to milled Wayne rat food. In addition, each rat was provided with a free source of liquid which contained .5 mg of morphine HCl in every milliliter. The solution vehicles were 2.5% sucrose water for three rats, 5% sucrose water for four rats, and 10% sucrose water for four rats. After 25 days of the above regimen, the three groups were presented with a choice test. That is, each group was given access to free food and their respective

sucrose-adulterated morphine solution in addition to free water. This situation was maintained for 13 consecutive days for all three groups. Daily measures of body weight and of liquid and food intake were taken. In order to guard against position preference, the location of water and sucrose morphine sources was determined randomly from day to day for each rat.

Beginning with Day 14 of the choice test and continuing through Day 22, a new manipulation was introduced for the group that had originally been maintained on .5 mg of morphine HCl in every milliliter of a 10% sucrose water. Specifically, each rat was provided with free access to food, a 10% sucrose water source, and a 10% sucrose water adulterated with .5 mg of morphine. Measures of body

weight, food, and liquid intake were taken daily.

RESULTS AND DISCUSSION

The results are presented in Fig. 1. The ordinate indicates the mean daily solution ingestion per S in milliliters. It is clear from Fig. 1 (left frame) that all three groups virtually ignored the water and maintained a high level of sucrose morphine intake. Analysis of variance indicated that the preference for sucrose morphine over water was statistically reliable for all three groups ($F = 64.88$, $df = 1/8$, $p < .01$). There seems to be an intake hierarchy based on the sucrose content of the solutions. That is, over the 13-day period, the 10% sucrose morphine was ingested most while the 2.5% sucrose morphine was ingested least. However, these apparent differences were not statistically significant.

Consideration of the data presented in the left frame of Fig. 1 points up, at the very least, the utility of the sucrose adulteration procedure in production of high voluntary ingestion of morphine solution by the rat. Thompson & Ostlund (1965) observed that their rats ingested an average of only 32.5 ml of a .5 mg/ml of morphine water solution, even after some 60 days of forced drinking. Therefore, adulterating the morphine solution with 10% sucrose increases the intake by nearly 300%. One obvious limitation of the sucrose adulteration procedure is that rats are very good caloric meterers (Khavari, 1970). However, our observations indicate no undesirable effects on the

Fig. 1. Left: Three groups of rats maintained on sucrose-adulterated morphine for 25 days ingested greater quantities of the solution than of water, during a 13-day choice test. Right: The highest sucrose concentration group was presented with sucrose morphine and the sucrose vehicle for an additional 9 days.

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rats' dietary regulation with sucrose concentrations as high as 10%.

The data presented in the right frame of Fig. 1 provide clear evidence for the development of sucrose morphine preference over the vehicle. During Day 14 of the choice test (the first day of opportunity for the rats to choose between 10% sucrose and 10% sucrose containing .5 mg/ml of morphine HCl), the rats ingested liquid from both sources. During Day 14 the Ss consumed 32.7 ml of sucrose morphine and 58.2 ml of the vehicle, on the average. However, beginning with Day 15 and continuing through Day 22, all Ss showed a clear preference for the morphine sucrose over the vehicle ($F = 10.54$, $df = 1/3$, $p < .05$).

Clearly, there are a number of advantages and limitations associated with the oral procedure. Some of the advantages are: (1) the economic

nature of the method, i.e., tedious and time-consuming injection and venous cannulation procedures are not necessary; (2) massive numbers of animals can be placed under this regimen with minimal care and effort requiring professional personnel; (3) the animals regulate their own intake of morphine by ingesting appropriate quantities of the solution. A possible disadvantage is that rats are excellent in measuring their daily caloric intakes. Therefore, there is an upper limit for sucrose concentration that can be employed to boost morphine intake. Noncaloric flavoring may serve as effective substitutes for sucrose. In our laboratory, we have found that hypotonic saline (.6%) is also a good morphine vehicle, but not as good as 10% sucrose. Also, both the peak and the maintenance levels of morphine achieved by the oral procedure may be different from those

obtained via injection of equivalent doses. Nonetheless, the above oral procedure appears to be a highly effective and economical method for studying various physiological and psychological parameters of morphine dependence.

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