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Small doses of morphine enhance voluntary intake of a solution of only ethanol and water

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Rats, subsequent to having an extensive history of intake of alcoholic beverages, were placed on a schedule of water deprivation. Each day, they were given a 2-h opportunity to take either a 6% solution of ethanol (6 g of ethanol and 94 g of tap water for each 100 g of fluid) or water. Across daily opportunities, intakes of the ethanol solution and water stabilized, with rats taking about 1.0 g/kg of ethanol. Then, immediately prior to some sessions, rats were given injections of either placebo, or 1.0 or 2.0 mg/kg morphine. On days of administration of morphine, rats took considerably more ethanol than on days of placebo administration, with a mean increment of about 0.9 g/kg. This finding supports results of similar experiments and lends credence to the idea that differential functioning of endogenous opioid systems may be a salient feature of differential intake of alcoholic beverages.

Across the last several years, our laboratory has been studying the effects of opioids on intake of solutions containing ethanol. We have found that small doses of morphine, methadone, and fentanyl (all agents that are agonists at opioid receptors) enhance the voluntary intake of solutions containing ethanol (Czirr, Hubbell, Milano, Frank, & Reid, 1987; Hubbell, Czirr, & Reid, 1987; Mudar, LeCann, Czirr, Hubbell, & Reid, 1986; Reid & Hunter, 1984). Naloxone, the classic antagonist at opioid receptors, reduces intake of ethanol solutions (Reid & Hunter, 1984), as does naltrexone (Altshuler, Phillips, & Feinhandler, 1980), the long-lasting antagonist. These basic observations have led to the development of a theory of alcohol abuse and alcoholism that emphasizes the salience of endogenous opioids with respect to whether or not individuals take "excessive" amounts of alcoholic beverages, and thereby suffer the toxic effects of ethanol.

We have found that morphine enhances intake of ethanol solutions by rats under a variety of conditions. Many of our tests of opioids' effects involve providing mildly water-deprived rats with an opportunity to take either water or a sweetened ethanol solution across a 1.5- or 2.0-h daily period. For the first few days of the regimen, rats take a daily ration of water and very little of the ethanol solution. Across days of presentation of solutions, they gradually increase their intake of the ethanol solution until, after about 3 weeks, they are taking about 2.0 g of pure ethanol per kilogram of body weight. This regimen of daily presentation of a palatable ethanol solution and water to water-deprived rats has a number of advantages with respect to the testing of the effects of drugs on ethanol intake. The period of intake is short enough to assess the drug's effects without confounding them with postdrug effects, and the amount of ethanol taken is substantial. Because, however, a palatable alcoholic beverage (e.g., a sucrose-sweetened ethanol solution) is used, there remains the possibility that an agent, such as morphine, might be enhancing intake of palatable solutions merely because of the additive (flavoring or additional calories) rather than the ethanol or because of some combination of the effects of the additive and ethanol. Although this, by itself, does not represent a serious problem for the applicability of conclusions to the human condition of alcoholism, since almost all alcoholic beverages consumed by people are treated to enhance their palatability, it seems necessary to show that morphine will enhance intake of an ethanol solution containing no particular flavoring, that is, simply pure ethanol and water. Rats, however, do not readily take solutions of only ethanol and water in large amounts. Consequently, we used rats that have an extensive history of alcohol intake and that take considerable amounts of ethanol in water.

One test of morphine's effects on intake of unflavored ethanol solution provided rats with only one solution to drink, that is, one containing ethanol. Morphine enhanced that intake (Hubbell et al., 1986). In the present study, rats with an extensive history of ethanol solution intake were presented a choice between either tap water or a solution of ethanol and tap water across a 2-h daily period. Prior to some sessions, either 1.0 or 2.0 mg/kg of morphine was administered. The results confirm that morphine enhances intake of unflavored ethanol solution.

METHOD

Subjects

Twenty-four male, Sprague-Dawley rats, purchased from Taconic Farms (Germantown, NY) and having an extensive history of drinking ethanol solution, were the subjects of this study. They had consumed a solution of 12% ethanol and 5% sucrose for 2 h/day for 20 days, after which they were switched to an unsweetened 6% ethanol solution

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for 8 days. Next, they were allowed constant access to tap water and 6% ethanol solution for 32 days, during which time some rats received infusions of morphine. Finally, 5 days before the start of these procedures, they were switched back to the 2 h/day drinking schedule, still having the opportunity to take 6% ethanol solution. The rats were divided into two groups of 12, one to receive 1 mg/kg of morphine, the other to receive 2 mg/kg of morphine.

The rats weighed a mean of 410.1 g at the start of these particular procedures. Throughout all of the procedures, they were individually housed in standard hanging cages in a colony room maintained at 24° C. The windowless colony room had 12 h artificial light per day, beginning at 0900 h. Food was always available and water was available daily, but often on a schedule of presentation.

Drugs, Solutions, and Apparatus

The ethanol solution was 6% ethanol (6 g of pure ethanol in 94 g of tap water). The morphine injections were given in two doses: 1.0 and 2.0 mg/kg (morphine sulfate in physiological saline). Placebos were injections of physiological saline. All injections were administered subcutaneously, 1.0 ml/kg.

Fluids were presented in glass bottles equipped with ballpoint sipping tubes. Bottles were weighed daily to the nearest 0.1 g before and after their presentation to determine amounts taken by rats. Ballpoint tubes prevent substantial evaporation (Myers, Ng, Marzuki, Myers, & Singer, 1984), but do not prevent some spillage as fluids are presented. Consequently, values obtained from weighing the bottles were corrected for spillage (Myers et al., 1984; Hubbell et al., 1986).

Procedure

First, the rats were placed on a daily deprivation schedule involving 22 h of fluid deprivation followed by 2 h of fluid presentation; that is, each day at 1100 h, rats were presented with water and ethanol solution. After 4 or 5 days of this particular schedule, the rats' intakes were stable, and injections were begun on the next day. Placebo injections were given on the first day, morphine injections on the next, and then placebo injections again on the third day. Effects that might be associated with a particular day were controlled for by beginning the series of injections for half of the rats one day after the other half.

Subjects' body weights and intakes of water and ethanol solution were tabulated. Total fluid intake was calculated as the amount of water taken plus the amount of ethanol solution taken. Preference ratios were also calculated (amount of ethanol solution taken/total amount of fluid taken), as well as grams of ethanol per kilogram.

RESULTS AND DISCUSSION

As expected, there was not much difference between the effects of 1.0 and 2.0 mg/kg of morphine. Across doses, morphine increased mean intake of the ethanol solutionby 85%; that is, with morphine they took a mean of 12.70 g, and with placebo they took a mean of 6.80 g across sessions. Morphine concomitantly decreased mean water intake by 28%. Consequently, preference ratios were increased under doses of morphine from 0.33 on days of placebo to 0.55 on days of morphine [$t(23) = 6.98$, $p < .0001$]. Results, in terms of grams per kilogram, are summarized in Figure 1. Interestingly, total fluid intake was not reliably increased.

The difference in consumption between days of administration of morphine and days of predrug placebo for the 12 rats receiving 1.0 mg/kg of morphine was 0.79 g/kg [$t(11) = 4.27$, $p < .005$], and the difference for the 12 rats receiving 2.0 mg/kg was 0.97 g/kg [$t(11) = 5.81$, $p < .0001$]. Both groups returned to their baseline levels of consumption on the day following morphine administration (Figure 1).

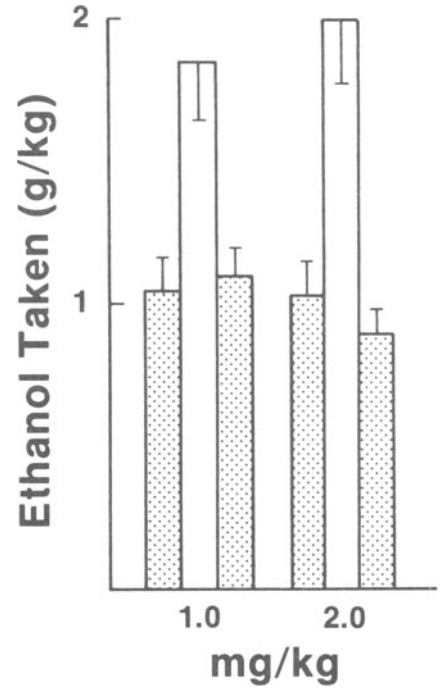

Figure 1. Mean grams (and *SEMs*) of pure ethanol taken per kilogram of body weight, by dose. Shaded bars represent intake on placebo days before and after the day of morphine administration (empty bar).

This demonstration that small doses of morphine enhance ethanol intake complements other data showing that morphine enhances intake of ethanol solutions in other circumstances. Small doses of morphine also enhance intakes of sweet (sucrose and saccharin) and salty solutions (Bertino et al., in press; Calcagnetti & Reid, 1983; Czirr & Reid, 1986). So morphine's effects are not exclusive to solutions containing ethanol. On the other hand, solutions containing ethanol are surely among those ingesta whose intake is enhanced by morphine.

Small doses of morphine enhance intakes of palatable solutions, including ethanol solutions. Naloxone decreases intakes (Reid, 1985). These basic findings form a foundation for the speculation that one or more of the endogenous opioid peptides may be critically involved in some instances of overconsumption of ingesta. Since surfeits of opioids seem to potentiate ingestion once begun (Czirr & Reid, 1986), the speculation is that the opioid peptides may be relevant to instances of binge consumption, including binge consumption of both flavored and unflavored ethanol solutions.

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