Effects of tolerance on intravenous morphine self-administration behavior

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After their operant level of leverpressing was determined, four groups of rats were given intravenous injections of either saline or morphine sulfate in daily dosages of 50, 100, or 300 mg/kg/day (divided among three equal doses for 3 days). Following these tolerance-producing treatments, all subjects were allowed to acquire a leverpressing behavior on a CRF schedule for intravenous injections (1.0 mg/kg) of morphine. In the 10-h acquisition sessions, both the number of infusions received and the amount of drug self-administered were directly proportional to the dosage used to induce tolerance.

The development of tolerance with repeated use is a characteristic feature of opiates which has been long recognized in the literature on human drug self-administration (Jaffe, 1970; Murphree, 1965; Wikler, 1953). Unfortunately, the analysis of tolerance as a factor in the self-administration of opiates has received little systematic attention in animal research.

Two studies on oral self-administration of morphine which compared only two conditions, tolerance vs. no tolerance, indicated that tolerant rats drank more morphine solution than did nontolerant ones (Kumar & Stolerman, 1973; Nichols, Headlee, & Coppock, 1956). Another study which employed multiple levels of tolerance, i.e., with maintenance doses of 0, 80, 140, or 200 mg/kg of intraperitoneal morphine, showed that rats drank increasing amounts of morphine solution up to the 140 mg/kg dose (Cappell & LeBlanc, 1971). No published report has involved tolerance as the independent variable when investigating intravenous opiate self-administration behavior. However, data from comparable studies in which subjects were tolerant (Weeks, 1962) and nontolerant (Smith, Werner, & Davis, 1974; Weeks & Collins, 1971) suggest that tolerant subjects self-administer more morphine.

The present research was conducted to characterize the effects of tolerance on acquisition of intravenous opiate self-administration behavior by rats.

METHOD

Subjects

Twenty adult male rats of Sprague-Dawley descent, weighing 400-500 g, were used as subjects. All were drug naive at the start of the experiment. Water and food were available ad lib throughout. All subjects were housed individually.

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Apparatus

Each rat was implanted with a chronic indwelling jugular catheter, which passed from the jugular vein subcutaneously to an exit on the upper back where it was attached to an external harness. By way of the harness, the catheter system was attached to a length of needle tubing which led to a leakproof swivel at the top center of the chamber. The opposite end of the swivel was connected by vinyl tubing to an infusion pump which delivered .023 ml of .9% saline solution or morphine sulfate solution in .25 sec each time it was activated. The experimental chamber, a plastic cylinder of 24 cm height and 25 cm diam, contained a response lever, food, and water. Each chamber was lighted and enclosed within a ventilated sound-attenuated compartment. Leverpresses were registered on electromechanical counters, while all programming was accomplished automatically with relay circuitry. For more details on the surgery, catheter, swivel, infusion system or chambers, see Smith and Davis, 1975.

Procedure

The subjects were placed in the self-infusion chamber and attached to the injection system via their external harness. A 1-h period was then allowed for adaptation to the chamber. Following adaptation, the operant level of leverpressing was determined for a 10-h period. During this time, each lever response was followed by a .25-sec intravenous infusion of .023 ml of saline. The subjects were then divided into four groups of five rats each. On the following 3 days, three intravenous injections were given at intervals of 8 h. Group 1 received only saline. The other groups all received a solution of morphine sulfate: Group 2, 16.67 mg/kg/injection (50 mg/kg in 24 h), Group 3, 33.34 mg/kg/injection (100 mg/kg in 24 h), and Group 4, 100 mg/kg/injection (300 mg/kg in 24 h).

On the day after the last of the tolerance-inducing injections, and on 2 subsequent days, the subjects were placed in the chambers for 10-h sessions with access to 1.0 mg/kg/injection of morphine.

RESULTS AND DISCUSSION

The mean number of infusions for the operant level and for morphine self-administration are shown in Figure 1. The data indicated that groups were equally matched for operant level of responding ($p > .05$). Following injections to induce tolerance, the number of infusions and the amount of morphine self-administered was an increasing function of the tolerance dose.

Statistical analysis showed all data for tolerance groups to be elevated significantly above the saline

Figure 1. Mean total infusions during initial operant level observation (Session 1) before tolerance infusions and during three drug-access sessions (Sessions 2, 3, 4) after tolerance infusions. Treatment groups representing different levels of morphine tolerance are identified according to doses on the right, 0 (saline) 50, 100, and 300 mg/kg, which indicate the daily tolerance doses of morphine given for 3 days.

group—50 mg/kg, $p < .01$; 100 mg/kg, $p < .001$; and 300 mg/kg, $p < .001$. These data also indicate that the number of infusions and the amount self-administered were directly proportional to the tolerance dose; i.e., as the tolerance dose was increased, more drug-taking behavior resulted. Statistical comparison of these groups shows a significant linear trend ($p < .01$). Thus, the present tolerance data supports that observed in earlier studies, i.e., tolerance produces increased drug-taking behavior.

The present discussion focuses completely on the tolerance aspects involved in the research. However, repeated injections of opiates confer both tolerance and physical (i.e., physiological) dependence. Physical dependence is known to amplify opiate-taking behavior (Schuster & Thompson, 1969; Schuster & Villarreal). Physical dependence was

readily apparent in the present research in that abstinence signs were observed during the course of and following the experiment. Thus, to infer that only tolerance was a factor in this study would not present a completely accurate account. At the present time, available technology does not adequately distinguish effects of opiate tolerance and physical dependence. As the two factors interact, it will be important for future research to explore these phenomena.

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