PHYSIOLOGY

Effect of Substance P on Intravenous Self-Administration of Morphine in Different Rat Strains

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We studied the effects of substance P on intravenous self-administration of morphine in WAG/G and Fischer-344 rats. By the end of week 2 the daily amount of self-administered morphine in WAG/G rats was higher than in Fischer-344 rats. Treatment with substance P markedly suppressed self-injection of morphine, particularly in low doses. The most pronounced effects were observed in Fischer-344 rats. Substance P did not change food-procuring behavior of animals in the same experimental chambers. Since the content of substance P in the hippocampus, hypothalamus, and midbrain of Fischer-344 rats is much lower than in WAG/G rats, and morphine addiction in Fischer-344 rats is less pronounced than in WAG/G rats, the degree of opiate addiction is not determined by the content of substance P in rat brain. However, in our experiments treatment with substance P abolished morphine addiction, particularly in animals with low content of this compound in the brain.

Key Words: *morphine; inbred rats; self-administration; attraction; substance P*

There are various methods for studying individual predisposition to the formation of pathological addiction to drugs (*e.g.*, opiates). Intravenous self-administration of morphine or heroin in inbred rats is the most widely used experimental model [4]. Our previous studies showed that WAG/G and Fischer-344 (F-344) rats differ in their sensitivity to analgesic and positive reinforcing effects of morphine [8]. We hypothesized that these rats also differ in the formation of pathological morphine addition.

It was demonstrated that neurokinin substance P (SP) is involved in the formation of opiate addiction. Intracerebral administration of SP activates the reinforcement system [2]. SP content in various midbrain regions increases in heroin-dependent rats waiting for heroin infusion [3]. Moreover, the content of N-terminal fragments of SP (SP_{1-7}) in the hypothalamus increases in morphine-dependent rats during abstinence [10]. SP and its receptor antagonists affect the syndrome of morphine withdrawal [5-7]. However, the effects of SP on pathological opiate addiction remain unknown. Our previous studies showed that WAG/G and F-344 rats markedly differ in the content of SP in various brain regions [1,9].

Here we studied the effects of substance P on behavioral reactions of intravenous morphine self-administration in WAG/G and F-344 rats. In the control series we evaluated the influence of substance P on instrumental food-procuring behavior.

MATERIALS AND METHODS

Experiments were performed on male F-344 (n=32) and WAG/G rats (n=32) weighing 200 g. One week before and during the experiment all animals were kept in individual chambers (25×11×20 cm) at constant temperature (21°C) and under conditions of a 12:12 h light-dark cycle (light 8.00-20.00). The rats

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had free access to water and standard mixed feed, but were deprived of food 2 days before the start of experiments.

After 48-h food deprivation the rats were placed in an instrumental chamber for 50 min (Lafayette Instruments Inc.). Pressing a lever delivered a single food pellet (1, 45 mg, P.S. Noyes Company Inc.). This was followed by the latency period (17 sec), during which lever pressing did not lead to food delivery. During this period the rats were in darkness. On days 1-2, 3-4, 5-7, and 8-12 the rats were food-reinforced after 1, 2, 3, and 5 lever pressing, respectively. After the fist series (12 days) the rats demonstrated stable food-procuring behavior. In home cages these animals received 12 g food.

On the 13th, 14th, and 15th days of the experiment 8 rats of each strain were intraperitoneally injected with 50 μg/kg SP 15 min before the behavioral trial. Control animals (8 rats of each strain) received isotonic NaCl. Food-procuring behavior was tested over the next 3 days.

After series I, 16 rats of each strain were narcotized with 100 mg/kg ketamine. Two-component synthetic catheters were implanted into the jugular vein. The intravenous part of catheters was a 25-mm Silastic tube (outer diameter 1.2 mm, Dow Corning Corp.). The tip of the catheter was localized in the superior vena cava. The other part of the catheters was a 55-mm vinyl tube (outer diameter 1 mm, Dural Plastic and Engineering). One end of the vinyl tube was connected with the intravenous part through a special adapter (Small Parts Inc.), and the other was fixed to the skin on the neck.

The rats were kept in individual cages and had free access to food and water for 7 days (recovery period). Then these animals were placed in instrumental chambers and food-procuring behavior was tested for 50 min. The free end of the catheter was connected with a fine pump (Harvard Apparatus) via a liquid rotational contact. After 5 lever pressings 100 μg morphine hydrochloride in 0.05 ml isotonic NaCl were delivered into the superior vena cava through the catheter. The rats were placed in instrumental chambers to study the behavior of intravenous morphine self-administration for 9 days. After this period all rats were characterized by stable morphine consumption. On days 10, 11, and 12 the rats received 50, 100, and 150 μg morphine after 5 lever pressings, respectively. During the next 3 days the animals were exposed to the same procedure. Eight rats of each strain were intraperitoneally injected with 50 μg/kg SP 15 min before the daily behavioral tests. Control animals (8 rats of each strain) received isotonic NaCl. Self-administration of morphine in 3 doses was studied for the next 3 days.

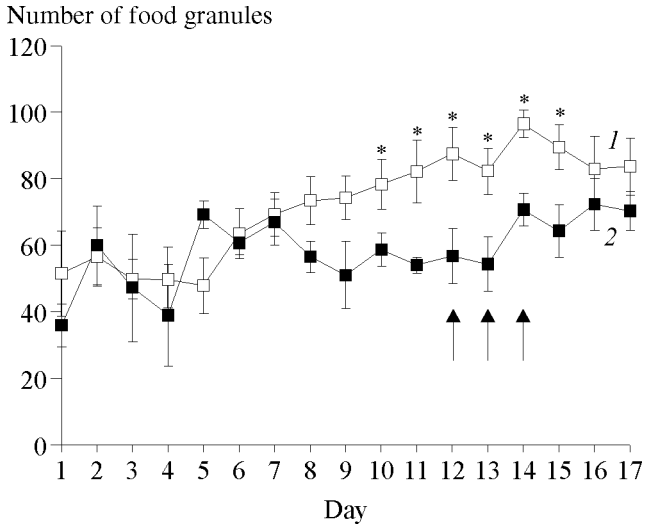

Fig. 1. Food-procuring behavior in WAG/G (*1*) and Fischer-344 rats (*2*) before, during (arrows), and after treatment with substance P. Here and in Fig. 2: *$p<0.05$ compared to Fischer-344 rats.

The results were analyzed by Student's *t* test.

RESULTS

Starting from day 8 of the experiment WAG/G rats consumed more food pellets than F-344 rats (over 1 h, Fig. 1). Rats of both strains easily retrained to obtain morphine injections instead of food reinforcement. However, 1 day after substitution of reinforces the number of lever pressings in F-344 rats was much higher than in WAG/G rats (27.20±4.25 and 18.85±2.75, respectively). In the next days the rate of lever pressing progressively decreased in F-344 rats, but remained unchanged in WAG/G rats.

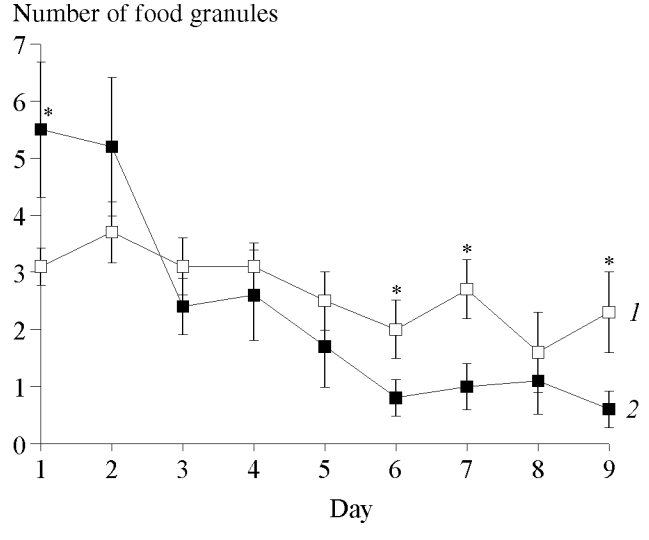

Fig. 2. Intravenous self-administration of morphine in WAG/G (*1*) and Fischer-344 rats (*2*).

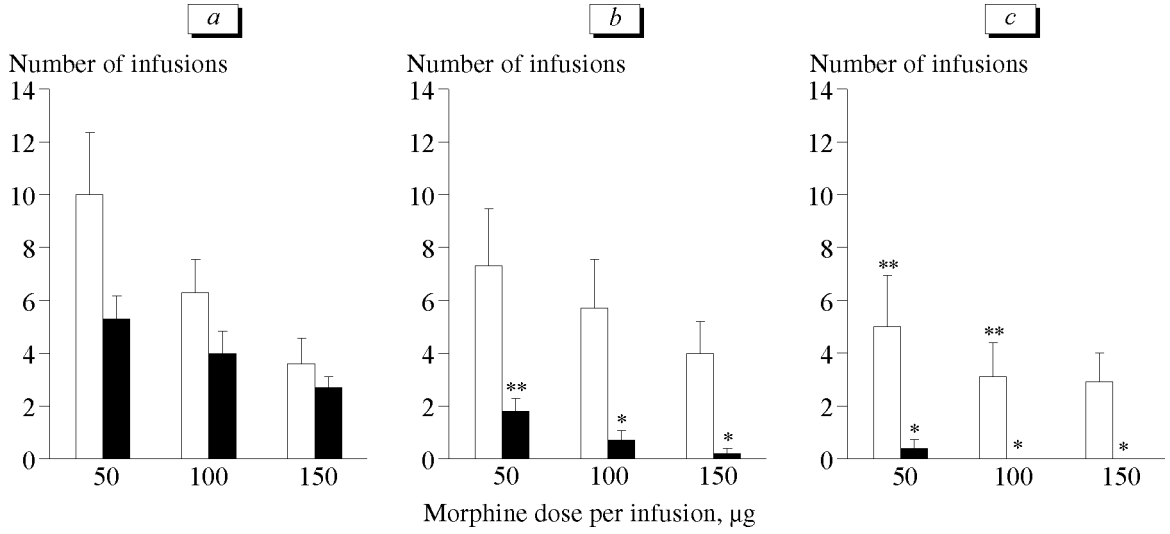

Fig. 3. Intravenous self-administration of morphine in various doses in WAG/G (light bars) and Fischer-344 rats (dark bars) before (*a*), during (*b*), and after treatment with substance P (*c*). *$p<0.01$ and **$p<0.05$ compared to the baseline.

One week after the start of morphine self-administration rats of both strains daily consumed constant amounts of morphine (Fig. 2). The number of lever pressings in WAG/G rats was much higher than in F-344 rats (17.5±4.5 and 6.65±2.00 during 1 trial, respectively). Decreasing the single dose of morphine to 50 μg was accompanied by an increase in the number of lever pressings. By contrast, increasing the dose of morphine to 150 μg was followed by a decrease in the number of lever pressings (Fig. 3, *a*). SP markedly suppressed morphine consumption. The rate of lever pressing to obtain morphine in various doses decreased, particularly 3 days after treatment with SP. SP most significantly suppressed self-administration of morphine in low doses. The inhibitory effect of SP was most pronounced in F-344 rats (Fig. 3). Self-administration of morphine in control animals remained unchanged.

Our previous studies showed that the content of SP in the hippocampus, hypothalamus, and midbrain in F-344 rats was much lower than in WAG/G rats [1,9]. However, pathological morphine addiction in F-344 rats is less pronounced than in WAG/G rats. These data suggest that the degree of pathological opiate addiction does not depend on SP content in rat brain. Nevertheless, treatment with SP abolished morphine addiction, particularly in animals with low content of this compound in the brain.

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