GENETICS

Inheritance of Morphine Sensitivity in (WAG/G - Fischer-344) F_1 Rats

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The effects of morphine on the pain sensitivity and motor activity of progeny obtained by different variants of crossing purestrain WAG/G and Fischer-344 rats are studied. Four groups of rats were investigated: WAG/G (male and female WAG/G rats were crossed), Fischer-344 (Fischer-344 male and female), F/W (Fischer-344 male, WAG/G female) F_1 hybrids, and W/F (WAG/G male, Fischer-344 female) F_1 hybrids. It is shown that the inheritance of individual features of sensitivity to the analgetic effect of morphine as well as of pain sensitivity is apparently sex-linked.

Key Words: *pain sensitivity; motor activity; morphine; inheritance; rat lines*

It is known that the degree of expression of the effect of opiates strongly depends on individual genetic features. There are individuals with high and with low sensitivity to morphine in mouse [2], rat [6], and human [4] populations. Pure-strain (inbred) animals are a convenient object for studying individual genetic features of the organism. For instance, we have shown [1,7] that WAG/G rats are significantly less susceptible than Fischer-344 rats to the effects of morphine on pain sensitivity and motor activity. Besides, morphine hardly has a positively reinforcing effect on WAG/G rats. Since pure-strain animals are homozygous, F_1 hybrids obtained from WAG/G and Fischer-344 rats must have an identical (except for the sex chromosomes) genotype, which consists of the WAG/G and Fischer-344 genotypes half-and-half. Hence, in the present investigation we aimed to study the effects of morphine on the pain sensitivity and motor activity of F_1 hybrids, in comparison with the WAG/G and Fischer-344 parental lines.

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MATERIALS AND METHODS

Experiments were carried out on male rats aged 2.5 months weighing 160 to 170 g obtained at the Laboratory of Neurobiology of Addictions, State Research Centre of Narcology, from WAG/G and Fischer-344 parental lines (*Stolbovaya* breeding centre of the Russian Academy of Medical Sciences). Four groups of rats were used in each series of experiments. There were 10 animals in each group. Group 1 (W/W) comprised rats obtained by crossing a WAG/G male and female. Group 2 (F/F) consisted of rats obtained by crossing a Fischer-344 male and female. Group 3 (W/F) was the progeny obtained from a WAG/G male and a Fischer-344 female. Group 4 (F/W) was the progeny obtained from a Fischer-344 male and a WAG/G female. The animals were reared maternally for 3 weeks, after which they were put on standard combined rations and water *ad libitum*. The light regime (12:12) and air temperature (20°C) were constant.

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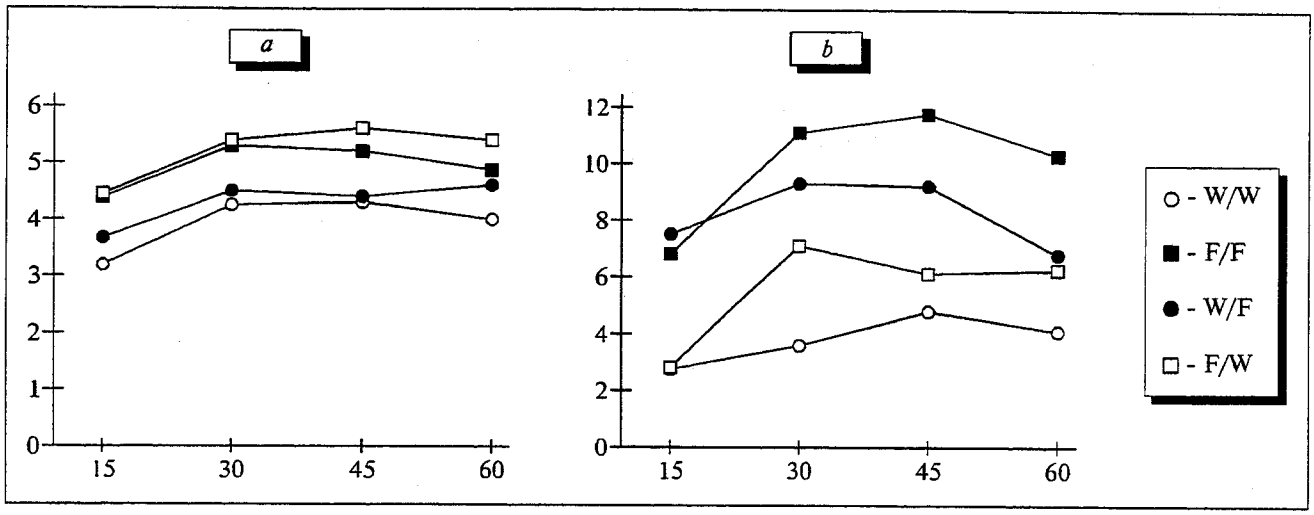

Fig. 1. Changes in pain sensitivity in different rat lines after injection of isotonic saline (*a*) and morphine (*b*). Ordinate: tail–flick latency (*a*) and difference of latencies before and after morphine injection (*b*), sec. Abscissa: time after injection of isotonic saline (*a*) and morphine (*b*), min.

To measure pain sensitivity we used the test of tail withdrawal (tail-flick test) from hot water (56°C). Four groups (W/W, F/F, W/F, and F/W) received an intraperitoneal injection of isotonic NaCl solution; another four identical groups were injected with morphine (5 mg/kg). Fifteen, 30, 45, and 60 min after injection the animal's tail was dipped into hot water to a depth of 4 cm and the latency of tail flick was measured.

Motor activity was measured during three minutes in the "open field" test, using a 41×41 cm^2 apparatus with automatic recording of the horizontal and vertical activity. Fifteen minutes before being placed in the apparatus, the four experimental groups were injected with isotonic NaCl solution intraperitoneally; the other four identical groups were injected with morphine (5 mg/kg).

Statistical processing of the results was performed with Microstat software. The significance of the differences was determined using the Student *t* test and Fisher *F* test.

RESULTS

The results corroborated our previous data [7] that Fischer (F/F) rats have a higher initial threshold of pain sensitivity and a higher reactivity to the analgetic effect of morphine than WAG/G (W/W) rats. We found that W/F and F/W F_1 hybrids differ from the parental lines in the threshold of pain sensitivity and morphine analgesia; the F/W and W/F hybrids also differ from one another. For example, F/W rats have the highest initial tail-flick latency, followed by (in descending order) the F/F, W/F, and W/W groups (F-4.84, $p<0.01$).

The latency in F/W hybrids reliably differs from that of W/W rats ($p<0.01$) and does not differ from that of F/F rats. The pain sensitivity of W/F hybrids is intermediate and does not differ either from that of W/W or from F/F rats (Fig. 1, *a*). The analgetic effect of morphine is highest in F/F rats, and then decreases in W/F, F/W, and W/W rats (F-7.75, $p<0.01$). At the same time, the analgetic effect is reliably higher in W/F hybrids in comparison with W/W rats ($p<0.05$) and does not differ from that in F/F rats. Conversely, the analgetic effect is reliably weaker in F/W hybrids ($p<0.05$) than in F/F rats ($p<0.05$) and does not differ from that in W/W rats (Fig. 1, *b*).

No linear differences were observed in the motor activity of animals. W/W, F/F, W/F, and F/W rats exhibited more or less the same amount of motor activity (F-0.054, $p>0.5$, Fig. 2). Never-

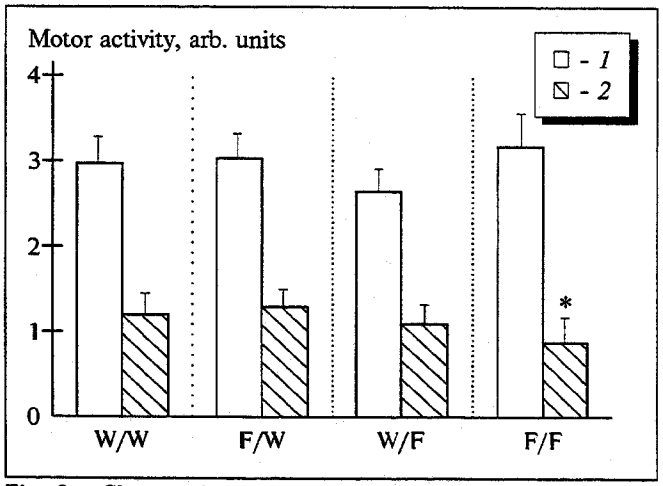

Fig. 2. Changes in motor activity in different rat lines after injection of isotonic saline (*1*) and morphine (*2*). *$p<0.05$ in comparison with the other groups.

theless, the morphine injection resulted in a reliably greater depression of motor activity in F/F rats than in W/W, W/F, and F/W rats ($p<0.05$). W/F and F/W hybrids did not differ from one another or from W/W rats in terms of the degree of motor activity depression (Fig. 2).

Thus, it may be speculated that the inheritance of individual features of sensitivity to the analgetic effect of morphine as well as of pain sensitivity is sex-linked. The genes that determine the expression of these features are located on the sex chromosomes. However, it is impossible to exclude the maternal influence on the progeny during gestation and rearing. These factors will be studied later. Inheritance of such a feature as a high sensitivity to the depressive (suppressing motor activity) effect of morphine is apparently not sex-linked.

Despite numerous data on the correlation between different effects of morphine (analgetic, euphoric, dependence, tolerance, etc.) [3,5,7], the findings suggest that individual sensitivity to different effects may be inherited independently. Hence, different types of sensitivity to individual manifestations of pharmacological activity of opiates may occur in an animal population.

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