covery and suggests that the number of animals with low resistance to acute hypoxia in a population is always equal to the number of highly resistant animals. The data indicate further that criteria of this resistance in a population are the geometric mean of survival time and the deviation of σ from τ; that a criterion of individual resistance of an animal to acute hypoxia is Student's parameter for that animal; and that the distribution of Student's parameter in a population is lognormal under any circumstances.

With the procedure described above, experimental findings can be treated in strict mathematical terms, avoiding the use of empirical coefficients. Moreover, the resistance to acute hypoxia can be recorded with the requisite accuracy at the population and individual levels by using a limited number of animals in the experiment. The use of this procedure can probably be extended to follow responses of animals to other adverse factors such as stress and environmental pollution.

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Participation of Opioid and Serotoninergic Brain Receptors in Amphetamine-Induced Stereotypy and Hyperthermy

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The inbred rat strains WAG and Fischer-344 were found to differ in the duration of amphetamine-induced stereotypy and the degree of hyperthermy elicited by this drug, the stereotypy lasting longer in WAG rats and the hyperthermy being more pronounced in Fischer-344 rats. A comparison of interstrain differences in the amphetamine effects, in receptor binding, and in the pharmacological activity of receptor agonists suggests that the μ-opiate system of the brain may be involved in the manifestation of amphetamine-induced stereotypy, while its serotoninergic system may mediate the elevation of body temperature caused by this drug.

Key Words: *amphetamine; stereotypy; thermoregulation; serotonin; morphine; clonidine*

Animals differ in their sensitivity to narcotic substances [3,4], and these differences appear to be governed by molecular/genetic mechanisms that determine neurochemical distinctions in the receptor binding and metabolism of narcotics and in the mediation of their effects. A pivotal role in the effects of psychostimulants is played by complex reactions of monoamine systems of the brain [1,2,5]. On the other hand, animals differing with regard to properties of the brain's opioid receptors and/or receptor binding of monoamines may also differ in their susceptibility to the development of addictive behavior [6].

Our previous studies [6] revealed differences in receptor binding between the WAG/G and Fischer-344 strains of rats. Thus, WAG rats were found to

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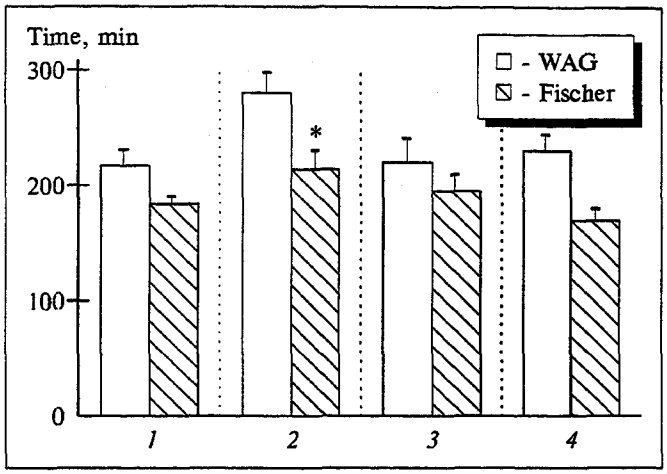

Fig. 1. Duration of amphetamine–induced stereotypy in WAG and Fischer rats injected intraventricularly with isotonic NaCl solution (*1*), morphine (*2*), clonidine (*3*), and serotonin (*4*). Here and in Fig. 2: the asterisk denotes a statistically significant difference from the control group given an intraventricular injection of isotonic NaCl solution.

have higher concentrations of μ-opioid and α_2-adrenergic receptors in the cerebral cortex than Fischer-344 rats but a lower affinity of the serotonin (5-HT_2) receptors for serotonin.

The purpose of the experiment described here was to assess, on the basis of these findings, the contribution of genetically determined differences in the characteristics of brain receptors between the WAG and Fischer-344 strains to the effects produced by amphetamine. More specifically, we were interested in studying the differences between WAG and Fischer-344 rats in the degree of amphetamine-induced stereotypy and hyperthermy and to see how stimulation of μ-opioid, α_2-adrenergic, and serotoninergic receptors would influence the

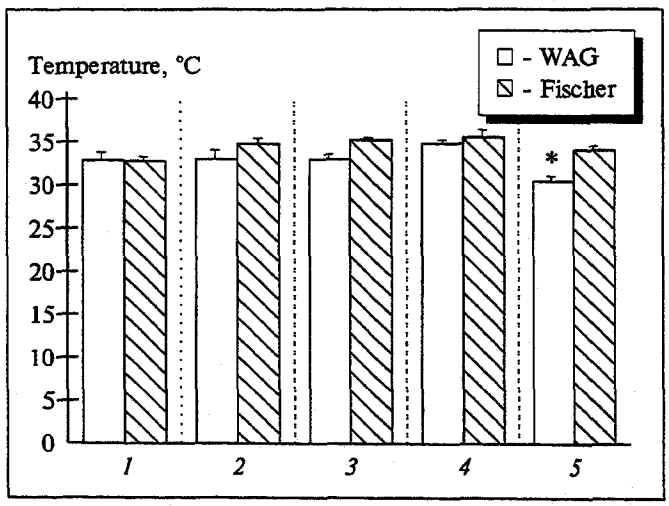

Fig. 2. Rectal temperature in WAG and Fischer rats before (*1*) and after intraperitoneal injection of amphetamine and intraventricular injection of isotonic NaCl solution (*2*), morphine (*3*), clonidine (*4*), and serotonin (*5*).

duration of amphetamine-produced stereotypy and the hyperthermic activity of this compound in the two strains.

MATERIALS AND METHODS

The experiment was conducted on male Fischer-344 and WAG rats, 64 animals of each strain (body weight 180-200 g), obtained by from the *Stolbovaya* Nursery of the Russian Academy of Medical Sciences. The rats were kept in cages, 8 animals in each, on a 12-hour lighting schedule at an ambient temperature of 20°C and had free access to food and water. Under Nembutal anesthesia (50 mg/kg), a stainless steel cannula 0.5 mm in diameter was implanted into a lateral brain ventricle of each rat (P=1.0 mm, L=1.5 mm, H=3.5 mm). Before the tests, rectal temperature was measured in all animals.

There were four pairs of test groups, each group consisting of 16 Fischer and 16 WAG rats. The first and second pairs received, respectively, an intraventricular (i.v.) injection of 1 μg of morphine and 10 μg of clonidine in 10 μl of isotonic NaCl solution; the third pair was given an i.v. injection of serotonin (5-HT_2, 0.5 μ) and the fourth pair (controls), 10 μl of a 0.9% NaCl solution by the same route. Immediately after the i.v. injection of the indicated substances, 8 rats of each group were injected intraperitoneally (i.p.) with 8 mg/kg of amphetamine dissolved in isotonic NaCl solution, while the remaining 8 rats received an i.p. injection of this solvent alone. Thereafter, all rats were placed in individual cages 0.3 m long, 0.2 m wide, and 0.2 m high, and the times of onset and termination of continuous stereotypy (sniffing, movements of the head and limbs, and licking or biting) were recorded. Rectal temperature was measured again 1.5 h after amphetamine injection.

The data were analyzed statistically with the t test for nonpaired comparisons.

RESULTS

The rats injected i.p. with isotonic NaCl solution and i.v. with this solution, morphine, clonidine, or serotonin did not show any stereotypic activity, whereas the other 8 rats of each group, which received an i.p. injection of amphetamine, exhibited stereotypy of varying duration. In the control group given an i.v. injection of isotonic NaCl solution, the stereotypy in WAG rats lasted longer than in Fischer rats (216.9±14.9 min *vs.* 183.0±6.4 min). The i.v. morphine injection led to a significant prolongation of stereotypy (to 213.9±18.5 min)

only in the WAG rats; no significant differences from the control group in the duration of stereotypy were found for the other test groups (Fig. 1).

The initial rectal temperature in WAG and Fischer rats was almost the same (32.87 and 32.79°C, respectively). Rats injected i.p. with isotonic NaCl solution and i.v. with this solution, morphine, clonidine, or serotonin showed no significant changes in rectal temperature from its initial value. The i.p. injection of amphetamine caused significant hyperthermy only in Fischer rats, whose rectal temperature rose to 34.79°C. No significant elevations in rectal temperature were recorded for the WAG rats (Fig. 2).

The i.v. injection of morphine or clonidine did not alter rectal temperature, whereas the i.v. injection of serotonin resulted in a significant fall only in the WAG rats (Fig. 2).

The results of this study led us to conclude that the differences between WAG and Fischer rats in the characteristics of receptor binding in brain membranes may contribute to the effects produced by amphetamine in these two strains. It appears that the μ-opiate system of the brain may be a substrate activating the stereotypic behavior elicited by amphetamine, and that its serotoninergic system may indirectly influence the mechanism of amphetamine-induced hyperthermy.

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