NEW BIOMEDICAL TECHNOLOGIES

Effects of Acute and Chronic Caffeine Intake on Intravenous Self-Administration of Morphine in Two Rat Strains

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Effects of acute and chronic caffeine intake on the level and pattern of morphine self-administration behavior in WAG/G and Fisher-344 rats were studied. Both acute and chronic caffeine intake decreased morphine self-administration only in WAG/G rats, which attested to increased sensitivity of these rats to reinforcing effects of morphine. Possible relationship between the observed changes and increased anxiety in rats receiving caffeine is discussed.

Key Words: *caffeine; morphine*; *dependence; intravenous self-administration, anxiety*

Caffeine produces various effects on the organism depending on the dose and method of administration. The effects of caffeine on anxiety in humans and animals are described in details [1,3,4,7,12]. It is now established that the mechanisms of anxiety are intimately related with the endogenous reinforcement system. Therefore, changes in anxiety can modulate the intake of psychotropic and narcotic drugs. This probably underlies mutual potentiation of the reinforcing effects of caffeine, alcohol, and nicotine [5,10]. There is evidence that caffeine modulates the pattern of cocaine and amphetamine abuse [6,11]. In animals, acute [8,9] and chronic caffeine intake [13] increases the sensitivity to nicotine, cocaine, and amphetamine.

We previously revealed a strong correlation between anxiety and susceptibility to opiomania in experimental animals [14,15]. It was established that Fischer-344 rats characterized by increased anxiety were more sensitive to some effects of morphine than easy-tempered WAG/G rats. However, WAG/G rats demonstrated more intensive self-administration of morphine [2].

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Here we studied the effects of acute and chronic caffeine intake on the intensity and pattern of intravenous morphine self-administration behavior in WAG/G and Fisher-344 rats.

MATERIALS AND METHODS

Experiments were carried out on 30 male WAG/G rats and 30 male Fisher-344 rats weighing 200 g. The rats were housed in individual home cages (25×11×20 cm) at 21°C and 12-h light-dark regimen (light from 08.00 to 20.00). Twenty rats of each strain had free access to food (standard fodder) and water and 10 rats of each strain received 0.1% caffeine solution instead of water.

Three weeks after the start of the experiment, the rats were trained intravenous morphine self-administration behavior as described elsewhere [2]. They were trained fivefold pressing a lever in a special instrumental chamber, which resulted in injection of 100 μg morphine hydrochloride in 0.05 ml 0.9% NaCl into the *vena cava superior* via an implanted catheter. During this period the rats continued to drink tap water or caffeine solution. The rats were placed in the experimental chamber for 1 h every day for 9 days. During this period all rats formed stable morphine self-administration behavior. After that the number of mor-

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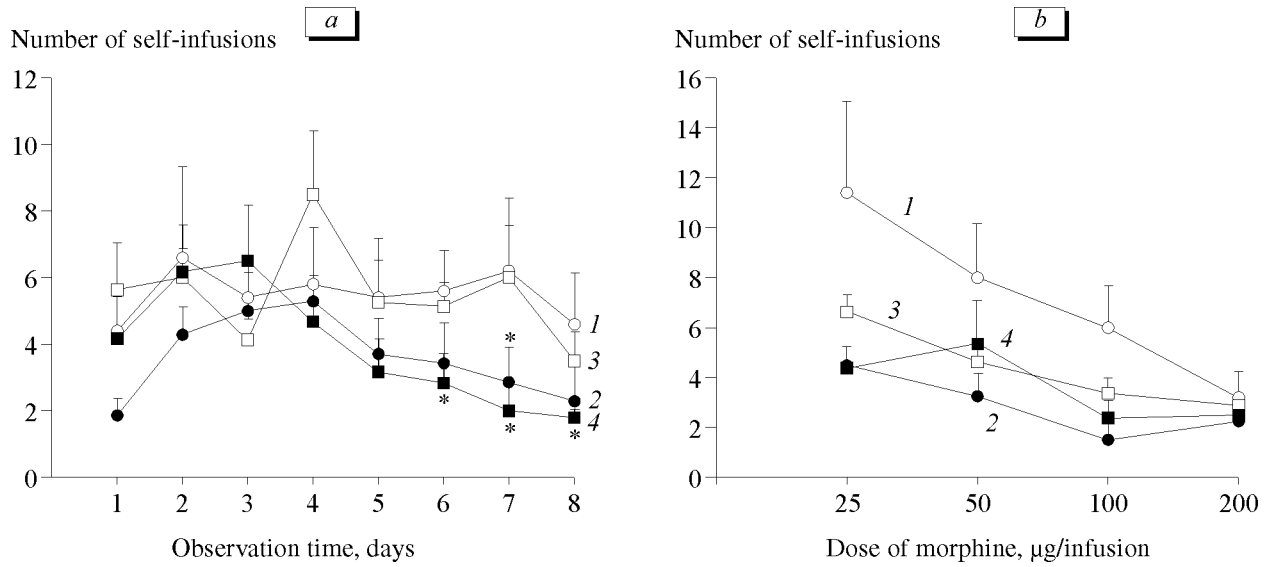

Fig. 1. Effects of chronic caffeine drinking (*a*) and intraperitoneal caffeine injection (*b*) on the morphine self-administration behavior in WAG/G (*1*, *2*) and Fisher-344 rats (*3*, *4*). *1*, *3*: water drinking (*a*) or injection of 0.9% NaCl (*b*); *2*, *4*: caffeine drinking (*a*) or injection (*b*). **p*<0.05: compared to rats of the same strain receiving tap water.

phine infusions (25, 50, 100, and 200 μg per infusion) was determined daily for 4 days. Caffeine (50 μg/kg) was intraperitoneally injected to 10 rats drinking tap water 15 minutes before the tests with morphine self-administration. Other rats were injected with 0.9% NaCl.

In rats drinking caffeine solution as the only source of water throughout the experiment, tests with different morphine doses were repeated after 3-day drinking tap water.

The data were statistically analysed using two-factor variance analysis and Student's *t* test.

RESULTS

Chronic caffeine intake almost did not affect the rate of acquisition of intravenous morphine self-administration responses: stable morphine intake was observed in all experimental groups on day 4 of learning. Only in WAG/G rats drinking caffeine solution the number of morphine infusions progressively decreased with time. Starting from day 6, the number of morphine infusions in this group was significantly lower than in WAG/G rats drinking water (Fig 1, *a*).

Analysis of self-administration of different doses of morphine in rats showed that the lower was the dose, the more infusions were self-administered per session (Fig 1, *b*). Considerable differences in sensitivity to the reinforcing effect of low doses of morphine were found between water-drinking rats of two strains (Fig 1, *b*). Thus, in WAG/G rats the number of self-infusions (25 μg morphine) was significantly higher than in Fisher-344 rats.

Intraperitoneal injection of caffeine reduced morphine self-administration in water-drinking WAG/G rats, but not in Fisher-344 rats (Fig 1, *b*).

Chronic caffeine intake also inhibited morphine self-administration behavior in WAG/G rats, but not in Fisher-344 rats. Inhibition of low dose morphine self-infusions was most prominent (Fig. 2).

In Fisher-344 rats, caffeine withdrawal after its chronic consumption enhanced self-administration of low doses of morphine, while WAG/G rats did not return to initial level of morphine self-administration (Fig. 2).

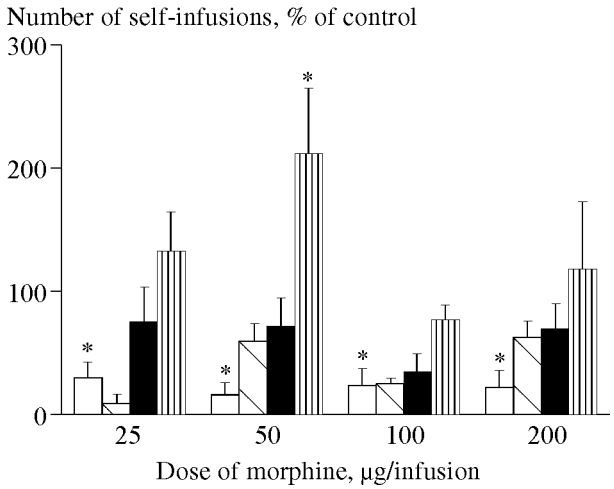

Fig. 2. Number of morphine self-infusions in WAG/G rats during caffeine drinking and withdrawal. Open and oblique-dashed bars: WAG/G rats; dark and vertically dashed bars: Fisher-344 rats. Open and dark bars: caffeine drinking; dashed columns: caffeine withdrawal. **p*<0.05 compared to the control.

Thus, both acute and chronic caffeine intake increased sensitivity to the positive reinforcing effect of morphine only in WAG/G rats. Our previous experiments showed that chronic drinking of 0.1% caffeine increased anxiety in WAG/G rats, but not in Fisher-344 rats [1]. It is likely that increased anxiety modulates the function of the endogenous reinforcement system and increased sensitivity to opiates and other psychotropic drugs.

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