EFFECT OF NICOTINE ON DEVELOPMENT OF AUDIOGENIC CONVULSIONS IN ANIMALS OF DIFFERENT AGES

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In experiments on young, adult, and old mice, rats, and guinea pigs, the effect of nicotine, injected intraperitoneally in doses of 3, 5, and 10 mg/kg, on the frequency and severity of audiogenic convulsions was studied. In rats and, to a lesser degree, in mice, the predisposition to convulsions was increased under the influence of nicotine, especially in young animals. In guinea pigs it was impossible to produce audiogenic convulsions, whether spontaneous or after injection of nicotine.

Epileptiform fits produced in rats and mice by an acoustic stimulus (audiogenic convulsions) have many mechanisms in common with convulsions in human epileptics. They form a very convenient model for trials of anticonvulsant drugs, for studying the mechanism of anticonvulsant treatment, and also for the elucidation of some aspects of the pathogenesis of epilepsy [1, 2, 4].

In this investigation the effect of nicotine on the incidence and severity of audiogenic convulsions was studied in rats, guinea pigs, and mice of different ages.

EXPERIMENTAL METHOD

Nicotine base, in the form of freshly prepared 0.3-0.5% solution, was injected intraperitoneally in doses of 3, 5, and 10 mg/kg for rats and 5, 10, and 25 mg/kg for mice. In response to injection of nicotine the animals' respiration rate was quickened, and they developed atony and tremor. This state lasted from 60 to 180 sec. The animals were placed in a special chamber 10-12 min after the injection, and at 30 sec a loud electric bell was switched on. The severity of the convulsion arising in response to the acoustic stimulus was assessed by a 4-point system. A mild convulsive reaction of 1-2 points was interpreted as a preepileptiform state, and a reaction of 3-4 points as an epileptiform fit. The following animals were used in the investigation: 380 female rats of 4 age groups – sexually immature (1 month), young (3-4 months), adult (11-12 months), and old (24-25 months); 320 female mice aged 2-3 months, 338 female mice aged 12-13 months, and 40 guinea pigs.

EXPERIMENTAL RESULTS

The convulsive response in intact animals to acoustic stimulation consisted mainly of running, and less frequently of nonlethal clonico-tonic fits, assessed as 2-3 points. Young rats were the most sensitive (the mean convulsion in these animals was 0.5±0.03 point), and the least sensitive were sexually immature (0.1±0.02 point) and old (0.18±0.04 point) animals. The mean severity of the convulsions in the adult animals was 0.32±0.06 point. This confirmed the results obtained in other models of convulsions [3]. Repetition of the tests 5-7 days later showed that the frequency and severity of the audiogenic convulsions in the rats were virtually constant.

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Injection of nicotine in doses of 3 and 5 mg/kg considerably increased the frequency and severity of the audiogenic convulsions ($P < 0.002$), particularly on account of the development of epileptiform fits. The most significant increase in frequency of the convulsions compared with that in the control animals was observed in young rats, and the least in sexually immature and adult rats. The increase in predisposition to convulsions bore a direct relationship to the dose of nicotine.

The mean severity of the convulsions after injection of nicotine in a dose of 3 mg/kg was 0.36±0.016 point in the sexually immature rats, 2.47 ± 0.21 point in the young, 1.53 ± 0.18 point in the adults, and 1.10 ± 0.20 point in the old rats, while after injection of nicotine in a dose of 10 mg/kg, the severity of the convulsions was 1.80 ± 0.30, 3.10 ± 0.10, 2.90 ± 0.80, and 3.0 ± 0.018 point, respectively.

With a higher dose of nicotine, the age differences in the severity of the audiogenic convulsions in the rats tended to disappear, and only in animals aged 1 month was their course significantly milder than in rats of the other age groups. The most marked increase in sensitivity of the rats to the audiogenic stimulus was observed 10-12 min after injection of nicotine. With an increase in duration of this interval the intensity of the convulsions was reduced, although it still exceeded the control level 25-30 min after injection. Repeated acoustic stimulation of the rats (both those which had previously had audiogenic convulsions and those resistant to the action of acoustic stimulation) usually did not evoke convulsions, indicating the relatively short duration of the effect of nicotine as a substance provoking epileptiform fits.

In experiments on young and old guinea pigs, spontaneous audiogenic convulsions were never observed. Intraperitoneal injection of nicotine in doses of 3, 5, and 10 mg/kg did not increase the sensitivity of the animals to acoustic stimulation. The resistance of guinea pigs to the action of acoustic stimuli is independent of the character of the audiofrequency generator [4, 5].

In experiments on 320 young mice, a spontaneous audiogenic convulsive reaction occurred in 25 animals, 9 of which (2.8%) had epileptiform fits, terminating fatally in 4 cases (1.25%). Of 338 mice aged 12-13 months, a convulsive response was observed in 14, of which 8 (2.3%) had epileptiform fits, terminating fatally in 5 cases (1.4%). The mean intensity of the convulsions in the young mice was 0.19±0.024 point, and in the old mice 0.11±0.014 point. Spontaneous audiogenic convulsions thus developed more frequently in young mice and followed a more severe course than in old mice ($P < 0.05$).

Nicotine increased the sensitivity of mice to audiogenic stimuli and provoked convulsions, but to a lesser degree than rats. The provocative effect of nicotine was weaker in old mice than in young ($P < 0.05$).

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