EFFECTS OF PSYCHOTROPIC DRUGS ON THE RAGE RESPONSES INDUCED BY ELECTRICAL STIMULATION OF THE MEDIAL HYPOTHALAMUS IN CATS

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Abstract—Effects of psychotropic drugs on the rage responses induced by electrical stimulation were investigated in cats with electrodes chronically implanted in the medial hypothalamus. Diazepam produced marked elevation in the threshold for directed attack and slight elevation in that for hissing. The inhibitory effect of etizolam on hissing was about 6 times as potent as that of diazepam. Anti-anxiety drugs such as diazepam, nitrazepam, lorazepam, clotiazepam and etizolam produced marked elevation in the directed attack threshold dose-dependently. The effect of chlorpromazine on directed attack was far less potent than that of anti-anxiety drugs. The anti-anxiety drugs used in this experiment had anti-pentetrazol activity in mice as well as muscle relaxant activity in cats. There were close correlations between the directed attack inhibition produced by the anti-anxiety drugs and both anti-pentetrazol activity and muscle relaxant activity. These results indicate that the above anti-anxiety drugs have a more potent inhibitory effect on the function of the medial hypothalamus than neuroleptic drugs. The inhibitory effect of anti-anxiety drugs on directed attack may be considered to correlate with clinical anti-anxiety effects.

It is widely accepted that the hypothalamus plays an important role in emotional behavior as well as in autonomic function. The rage response induced by electrical stimulation of the medial hypothalamus in cats is a well-organized emotional behavior (1). The hypothalamus has been considered to be a major site of action of psychotropic drugs (2), but there are only a few drug studies dealing with the rage response.

The present experiment was carried out to investigate i) the action of the psychotropic drugs on the rage response induced by electrical stimulation of the medial hypothalamus in cats, and ii) the correlation between the rage response inhibition produced by the drugs and both anti-pentetrazol activity in mice and muscle relaxant activity in cats.

Materials and Methods

Animals: Mongrel cats of both sexes weighing 2.4–3.0 kg and male dd mice weighing 20–25 g were used.

Drugs: The test drugs used were diazepam, nitrazepam, lorazepam, clotiazepam, etizolam, haloperidol and chlorpromazine, all of which were synthesized in our laboratories. The chemical structures of clotiazepam and etizolam are shown in Fig. 1.

Rage response test: Seventeen tame adult cats were implanted with electrodes chronically under pentobarbital anesthesia using a stereotaxic instrument. The stereotaxic coordinates were A: 10.0, L: 1.5, and H: −5.5 mm according to the atlas of Snider and
Electrodes were made of stainless steel wire, 0.19 mm in diameter, insulated with glass capillaries except for the tip. A stainless steel wire was fixed through the frontal sinus as an indifferent electrode for monopolar stimulation. These electrodes were connected to a socket and fixed to the skull with dental cement. After recovery from the operation, the cats were placed in an observation box (50×40×30 cm). The hypothalamic electrode was stimulated by a 60 Hz sine wave for 5 sec at 1 min intervals. During the electrical stimulation, the experimenter provoked the cat by bringing his face and hands close to the animal through the transparent plexiglas of the observation box. The thresholds for both hissing and directed attack were determined as the lowest stimulation intensity which elicited a response in three consecutive trials. The threshold changes were measured following oral or intraperitoneally cumulative administration of the drug. At least 1 week was allowed to elapse between test sessions. The ED50 was calculated by the regression line method as the dose which increased the threshold to 50% of the control value. After completion of the experiment, the location of the electrode tip was examined histologically.

Anti-pentetrazol test: Groups of 7 mice were administered intraperitoneally with each test drug and 15 min later given pentetrazol (150 mg/kg, s.c.). The ED50 was calculated by the probit method as the dose which prevented lethality in half the animals for 30 min after the pentetrazol injection.

Muscle relaxant test: Groups of 4–22 cats were given oral doses of each test drug in gelatin capsules. Muscle relaxant activity was estimated hourly in animals picked up by the scruff of the neck. Muscle relaxation was judged positive when the angle between abdomen and femur became obtuse. The minimum ED50 was determined by the probit method as the dose which caused muscle relaxation of legs in half the cats.

Results

Seven of the 17 cats were subjected to histological examination. The electrode tips examined on these seven were located at the ventromedial hypothalamic nucleus. The cats used in this experiment displayed typical rage responses. The behavioral patterns during hypothalamic stimulation were as follows: With relatively weak stimulation (below 1 v), pupil dilation, piloerection, salivation, ear-retraction and growling were induced. During electrical stimulation, the animal looked all around and sometimes stood up. Hissing was induced with somewhat strong stimulation (about 1 v). Soon after onset of stimulation, the animal stood up and took a threatening posture. With higher stimulation (1–1.5 v), directed attack was induced. Immediately after onset of stimulation, the animal stood up and arched its back, then attacked vigorously the experimenter with its foreleg. As the behavioral difference between hissing and directed attack was obvious, the effect of the drugs on each response could be estimated separately.

In the preliminary experiment, the effects of psychotropic drugs on hissing and directed attack were investigated in a cat. Threshold determination was made 1 hr after oral administration of each test drug. Diazepam (1 mg/kg) as well as etizolam (0.25 mg/kg) produced marked elevation in the threshold
for directed attack and slight elevation in that for hissing. Haloperidol and chlorpromazine did not change the thresholds for hissing and directed attack at the dose of 1 mg/kg.

The dose-response curves of diazepam on the thresholds for hissing and directed attack are shown in Fig. 2. Threshold determination was made 1 hr after oral administration of the drug. Diazepam produced marked elevation in the threshold for directed attack and slight elevation in that for hissing. The ED50 (its 95% confidence limit) for directed attack was 0.41 (0.28–0.64) mg/kg. The hissing threshold increased by 34% at the dose of 1 mg/kg.

The dose-response curves of diazepam and etizolam on the threshold for hissing are shown in Fig. 3. Threshold determination was made 1 hr after oral administration of each test drug. These drugs elevated the threshold for hissing dose-dependently. The ED50 determined graphically as the dose which increased the threshold to 50% of the control value was 3.6 mg/kg for diazepam and 0.66 mg/kg for etizolam. Anti-anxiety drugs suppressed hissing at relatively high doses.

Effect of psychotropic drugs on directed attack was investigated in groups of 3–5 cats. Intraperitoneal administration of each drug was made cumulatively at 2 hr intervals. The threshold determination was made 1 hr after each injection. The dose-response curves of the drugs on the threshold for directed attack are shown in Fig. 4. The anti-anxiety drugs produced marked elevation in the threshold for directed attack. The potency of clotiazepam was almost equivalent to that of diazepam. Nitrazepam and lorazepam were more potent than diazepam. Etizolam was the most potent. Chlorpromazine was far less potent than the anti-anxiety drugs. The ED50 (its 95% confidence limit) of chlorpromazine was 5.0 (3.4–8.3) mg/kg.

The anti-anxiety drugs showed marked...
Table 1. Effects of anti-anxiety drugs on the anti-pentetrazol test in mice, muscle relaxant test in cats and directed attack response in cats

| Drugs  | Anti-pentetrazol effect ED50 mg/kg, i.p. (mice) | Muscle relaxant effect ED50 mg/kg, p.o. (cats) | Inhibition of directed attack ED50 mg/kg, i.p. (cats) |
|--------|-----------------------------------------------|------------------------------------------------|--------------------------------------------------|
| Diazepam | 0.46 (0.42–0.52) | 0.48 (0.16–0.76) | 0.35 (0.25–0.63) |
| Nitrazepam | 0.25 (0.21–0.29) | 0.61 (0.42–1.15) | 0.21 (0.16–0.58) |
| Lorazepam | 0.06 (0.05–0.07) | 0.14 (0.10–0.20) | 0.09 (0.07–0.26) |
| Clotiazepam | 0.46 (0.35–0.62) | 0.57 (0.35–1.73) | 0.32 (0.21–0.52) |
| Etizolam | 0.08 (0.05–0.11) | 0.10 (0.06–0.15) | 0.05 (0.03–0.12) |

Fig. 5. Correlation between the inhibitory effect on directed attack response and both anti-pentetrazol activity and muscle relaxant activity.

Discussion

Electrical stimulation of the medial hypothalamus in cats induced typical rage responses such as hissing and directed attack. Nakao (1) reported that directed attack was induced by electrical stimulation of the ventromedial hypothalamic nucleus and that hissing without development of attack was evoked from the perifornical region of the medial hypothalamus. The electrode tips identified in this experiment were located at the ventromedial hypothalamic nucleus. Electrical stimulation of these electrodes induced both hissing and directed attack. The threshold for hissing was lower than that for directed attack. Therefore, the effects of the drugs on hissing and directed attack can be estimated separately. Diazepam increased the directed attack threshold more markedly than the hissing threshold. The ED50 of diazepam for directed attack was 0.41 mg/kg and that for hissing was 3.6 mg/kg. The inhibitory effect of diazepam on directed attack was about 9 times as potent as that on hissing. Etizolam elevated the threshold for hissing dose-dependently, and the potency of this drug was about 5 times as potent as that of diazepam. Effects of psychotropic drugs on the rage response induced by electrical stimulation of the medial hypothalamus in cats have been...
RAGE RESPONSES AND PSYCHOTROPIC DRUGS 889

reported by a few investigators. Baxter (4) reported that chlordiazepoxide (5–20 mg/kg, i.p.) did not change the hissing threshold. On the other hand, Funderburk et al. (5) found that chlordiazepoxide (10 mg/kg, i.p.) raised the hissing threshold by about 30%. These results together with the result presented in this paper indicate that anti-anxiety drugs suppress hissing at relatively high doses.

The reports which have dealt with the action of neuroleptic drugs on hissing are conflicting. Funderburk et al. (5) reported that chlorpromazine lowered the threshold for hissing. Baxter (6) found that 5 mg/kg of chlorpromazine did not change the hissing threshold. On the other hand, Maeda (7) reported that chlorpromazine and haloperidol elevated the hissing threshold. In the present experiment, chlorpromazine and haloperidol did not change the hissing threshold at the dose of 1 mg/kg. This result is consistent with the finding of Murasaki et al. (8). They found that haloperidol did not change the threshold for hissing. It is considered that neuroleptic drugs do not significantly affect hissing.

It has been reported that diazepam produced marked elevation in the threshold for directed attack induced by electrical stimulation of the ventromedial hypothalamic nucleus (7, 8). In the present experiment, benzodiazepines (diazepam, nitrazepam, lorazepam) as well as thienodiazepines (clotiazepam, etizolam) increased the directed attack threshold dose-dependently. These data indicate that anti-anxiety drugs markedly act on the site or the pathway displaying directed attack. Maeda (7) suggested that diazepam suppressed the afferent pathway of the directed attack and the mode of action of this drug was different from that of neuroleptic drugs. Chlorpromazine increased the directed attack threshold at high doses. Following the injection of chlorpromazine, the cats became severely sedated. Ataxia was also observed. Therefore, the effect of chlorpromazine on directed attack may be considered to be nonspecific. In this experiment, each drug was administered cumulatively at 2 hr intervals. Consequently, it is considered that the cumulative effect of the drug cannot be ignored. The inhibitory effect of diazepam on directed attack was investigated by oral administration once a week as well as by intraperitoneally cumulative administration at 2 hr intervals. The ED50 of the former was 0.41 mg/kg and that of the latter was 0.35 mg/kg. There was no significant difference between the former and the latter, so the cumulative effect was not so marked, if any.

From these results, it is concluded that directed attack is inhibited markedly by anti-anxiety drugs.

Zbinden and Randall (9) reported a detailed review on the pharmacological profile of benzodiazepines and on the relationship between clinical observations and animal pharmacology. They pointed out that anti-pentetrazol activity in mice as well as muscle relaxant activity in cats correlated well with clinical anti-anxiety effects. The anti-anxiety drugs used in this experiment had remarkable activity in these tests. To clarify the relationship between the inhibitory effect on directed attack and both anti-pentetrazol activity and muscle relaxant activity, the correlation between the two parameters was examined. There were close correlations between the parameters (r=0.99 for anti-pentetrazol activity and r=0.84 for muscle relaxant activity). Thus the inhibitory effect of anti-anxiety drugs on directed attack might be considered to correlate with clinical anti-anxiety effects.

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