INDIVIDUAL DIFFERENCE IN THE EFFECT OF DRUGS IN RELATION TO THE TISSUE CONCENTRATION OF DRUGS

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Received for publication November 11, 1968

It has been reported that the alteration in the effect of various drugs is often related to the alteration in the rate of drug-metabolism (1-10). For example, the administration of the phenobarbital and various drugs markedly decreased the effects of numerous drugs through increases in the activities of drug-metabolizing enzymes of liver microsomes (1-5). On the other hand, the effects of various drugs were increased in fasted or low protein diet fed rats through decreases in the activities of drug-metabolizing enzymes (6, 7).

It has been reported that species and sex differences in the effects of drugs are often related to the difference in the rate of drug metabolisms (1, 8-11).

It is well known that there are marked individual differences in the effects of various drugs in animal and clinical experiments. On the other hand, it has been considered that such individual differences may be due to differences in the sensitivity of the target organs. However, there are no direct evidence for supporting such opinion on the basis of the drug level in the target organs. The present study, therefore, is designed to determine whether the individual differences in the effects of pentobarbital and zoxazolamine are correlated to the difference in the sensitivity or in the drug level of the target organ.

METHODS

Female rats of Wistar strain, weighing about 180-200 g, were used. Pentobarbital sodium was dissolved in distilled water and zoxazolamine was suspended in 0.5% carboxymethylcellulose solution. The drugs were given intraperitoneally in volume of 2 ml/kg.

Experimental schedule

A) One-hundred seventy-eight rats were treated with pentobarbital sodium (30 mg/kg, i.p.) or zoxazolamine (110 mg/kg, i.p.). They were killed by exsanguination at the end of narcosis or paralysis and the concentration of drugs in the serum and brain was determined. The loss of righting reflex was used as the criteria of narcosis or paralysis.

B) Eighty-one rats were numbered and treated with pentobarbital sodium (22 mg/kg, i.p.) or zoxazolamine (85 mg/kg, i.p.) and were divided according to the degree of narcosis or paralysis. Fifteen or thirty minutes after the drug administration they were killed for the determination of the concentration of drugs in the serum and brain.

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Preliminary account of this study was presented at the 33rd Kanto Regional Meeting of the Japanese Pharmacological Society (October, 1965) and published briefly in *Folia pharmac. jap.* **62**, 129 (1966).

Determination of drug concentration

The serum was separated by centrifugation and the brain was homogenized with 2 volumes of distilled water. One ml of the serum and 3 ml of the brain homogenate were used for the analysis.

Pentobarbital and zoxazolamine were determined according to the method of Brodie *et al.* and of Conney *et al.*, respectively (12, 13).

RESULTS

1. Individual difference in the concentration of pentobarbital in the brain and serum at the end of narcosis

The duration of pentobarbital narcosis (30 mg/kg, i.p.) markedly differed from one rat to another (Figs. 1 and 2). Indeed, the largest difference in the duration of narcosis was about 6 times. Therefore, it is expected that if the difference in the duration of narcosis is due to the difference in the sensitivity of the central nervous system, the brain and serum concentrations of pentobarbital in the rats which were recovered in early time should be higher than those in the rats which were anesthetized for long time. However, the concentration of pentobarbital in the brain and serum at the end of narcosis was about the same in the all rats (Figs. 1 and 2). The regression equation between the duration of narcosis and brain pentobarbital concentration was expressed as $Y = 15.84 \pm 0.00776X$. These results indicate that the individual difference in the duration of pentobarbital narcosis is correlated to the rate of decrease of the drugs in the brain (3).

FIG. 1. Individual difference in the concentration of pentobarbital in the brain at the end of narcosis.

Seventy-two rats were treated with pentobarbital sodium (30 mg/kg, i.p.) and the rats were killed at the end of narcosis and the concentration of pentobarbital in the brain was determined. The results are expressed as the concentration of pentobarbital sodium in the brain at the end of narcosis.

FIG. 2. Individual difference in the concentration of pentobarbital in the serum at the end of narcosis.

See the legends for Fig. 1.

2. *Individual difference in the concentration of zoxazolamine in the brain and serum at the end of paralysis*

The duration of zoxazolamine paralysis (110 mg/kg, i.p.) markedly differed from one rat to another (Figs. 3 and 4). Indeed, the largest difference in the duration of paralysis

FIG. 3. Individual difference in the concentration of zoxazolamine in the brain at the end of paralysis.

Ninety-six rats were treated with zoxazolamine (110 mg/kg, i.p.) and the rats were killed at the end of paralysis and the concentration of zoxazolamine in the brain was determined.

FIG. 4. Individual difference in the concentration of zoxazolamine in the serum at the end of paralysis.

See the legends for Fig. 3.

FIG. 5. Individual difference in the concentration of pentobarbital in the brain in relation to the drug action.

Thirty-three rats were treated with pentobarbital sodium (22 mg/kg, i.p.) and 15 minutes later the rats were divided into the group of narcosis and non-narcosis and the rats were killed and pentobarbital concentration in the brain was determined. The results are expressed as the concentration of pentobarbital sodium. ● : Narcosis, ○ : Non-narcosis.

FIG. 6. Individual difference in the concentration of pentobarbital in the serum in relation to the drug action.

See the legends for Fig. 5.

was about 7 times. However, the concentration of zoxazolamine in the brain and serum at the end of paralysis was about the same in the all rats (Figs. 3 and 4). The regression equation between the duration of paralysis and brain zoxazolamine concentration was expressed as $Y = 79.2 \pm 0.006 X$. These results indicate that the individual difference in the duration of zoxazolamine paralysis is correlated to the rate of decrease of the drugs in the brain.

3. Individual difference in the concentration of pentobarbital in the brain and serum in relation to drug action

After the administration of 22 mg/kg of pentobarbital, the rats were divided into two groups according to the degree of pentobarbital effect (Figs. 5 and 6). The concentration of pentobarbital in the serum and brain was higher in the group under narcosis than in the group under non-narcosis. These results again suggest that the individual difference in the duration of pentobarbital narcosis is probably correlated to the concentration of drugs in the brain.

The difference in the brain concentration may be due to the difference in the rate of absorption, in the distribution and in the rate of drug-metabolism.

4. Individual difference in the concentration of zoxazolamine in the brain and serum in relation of drug action

After the administration of 85 mg/kg of zoxazolamine, the rats were divided in the three groups according to the degree of zoxazolamine effect (Figs. 7 and 8). The concentration of zoxazolamine in the serum and brain was higher in the group under paralysis

FIG. 7. Individual difference in the concentration of zoxazolamine in the brain in relation to the drug action.

Forty-seven rats were treated with zoxazolamine (85 mg/kg, i.p.) and 30 minutes later the rats were divided into the group of paralysis, non-paralysis and walking and the rats were killed and zoxazolamine concentration in the brain was determined. ● : Paralysis, ○ : Non-paralysis, x : Walking.

FIG. 8. Individual difference in the concentration of zoxazolamine in the serum in relation to the drug action.

See the legends for Fig. 7.

than in the group under non-paralysis and it was very low in the group under walking. These results again suggest that the individual difference in the duration of zoxazolamine paralysis is probably correlated to the concentration of drugs in the brain.

DISCUSSION

The durations of pentobarbital narcosis and zoxazolamine paralysis were markedly different among the rats of the same body weight and age which are apparently in the same condition. However, the concentrations of the drugs in the brain and serum at the

end of narcosis or paralysis were almost the same in these rats. If the difference in the duration of narcosis or paralysis was due to the difference in the sensitivity of the central nervous system, the concentrations of drugs in the brain and serum in the rats recovered at early time were should be higher than in those recovered after prolonged narcosis or paralysis. Therefore, the results of the present investigation suggest that there are no clear differences in the sensitivity of the central nervous system to the drugs and the rate of drug metabolism is probably more important factor for the determination of the duration of the drug actions.

Although the concentration of drugs in the whole brain is assumed to be not exactly represented the concentration of drugs at the sites of drug action, there is no concrete evidence that the distribution of drugs among different regions is altered under different conditions of animals. The effects of pentobarbital and zoxazolamine at short time after the injection are clearly correlated to the concentrations of the drugs in the brain and serum.

These results clearly suggest that the concentration of drugs at the site of drug actions is an important factor for the determination of drug actions. Therefore the difference in the amount of the injected drugs, in the rate of absorption, in the distribution and in the rate of metabolism are important factors for the appearance of the individual difference in the drug actions.

Mitoma *et al.* recently reported that there was clear correlation in each rat between the duration of hexobarbital narcosis and the activity of hexobarbital metabolism by liver microsomes (14). These results accord with the present observation.

Further study will be required to discriminate whether the individual difference in the drug action is due to the difference in the sensitivity of the target organ or due to the difference in the drug concentration at the site of the drug action.

SUMMARY

1. The duration of pentobarbital narcosis varied about 6 times from one rat to another, but the concentration of pentobarbital in the brain and serum at the end of narcosis was about the same.
2. The similar results were obtained from the rats given zoxazolamine.
3. The concentration of pentobarbital in the brain and serum at 15 minutes after the administration of low dose of the drug was much higher in the narcotizing group than in the non-narcotized group.
4. The similar results were obtained after the administration of zoxazolamine between the paralyzed group, non-paralyzed group and walking group.
5. These results suggest that the individual differences in the effect of pentobarbital narcosis and zoxazolamine paralysis are probably due to the differences in the concentration of drugs in the target organ through the differences in the rate of absorption, in the distribution and metabolism of the drugs. The individual differences in the sensitivity of the central nervous system to drugs, if exist, does not seem to be main factor.

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