SEASONAL RHYTHMS OF REACTIVITY OF MUSCLES TO AMOBARBITAL

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The duration of action of amobarbital (100 mg/kg, intraperitoneally) 2 days in succession was studied in 358 male albino mice. The experiments were carried out monthly for 4 years. The action of amobarbital was more prolonged in the spring and fall. In summer and winter it was shorter than the annual mean. The development of tolerance (a decrease in the duration of action of amobarbital on the 2nd day of administration) also showed seasonal changes, but only one maximum was observed. Tolerance was most marked during the spring.

In the last two decades interest in the study of rhythmic changes in biological processes has increased [2, 3, 7, 8, 10, 11, 13]. Periodic rhythmic changes, diurnal and seasonal, are observed in the hormonal activity, metabolism, and reactivity of the organism and also in the action of drugs [3].

In the course of 4 years (1967-1970) observations on seasonal changes in the duration of action of amobarbital on albino mice have been made in the Department of Pharmacology at Tartu University. The object of the investigation described below was to study this phenomenon in greater detail.

EXPERIMENTAL METHOD

To supplement the previous findings systematic experiments were carried out for 15 months (December, 1969 to February, 1971) on male albino mice (25-50 mice were used each month). Experiments were performed on 358 animals altogether (each mouse was used only once in the experiments). Amobarbital was injected intraperitoneally in a dose of 100 mg/kg on two consecutive days. The duration of action (the animals lay on their side) was determined on each day of the experiment. All experiments were carried out at the same time of day (from 9 to 11 A.M.), monthly, in the middle of the month. All mice were kept and fed under standard conditions. During the experiment the mice remained on a warmed litter at an atmospheric temperature of 25°C.

EXPERIMENTAL RESULTS

When two injections of amobarbital were given, the duration of its action on the second day was shorter, indicating the appearance of tolerance [4].

The duration of action of amobarbital on both days of the experiment varied with the month, so that there was agreement, in principle, between the observations made in different years. The mean results for 4 years are illustrated in Fig. 1 in the form of a polar diagram on which the duration of action of the hypnotic in minutes is plotted along the radii which represent the months. The difference between the extreme values (minimum—maximum) is statistically significant ($P < 0.05$).

Two cycles are observable on the diagram: the first with a maximum in the spring months, the second with a maximum in the fall; in summer and winter the action was shorter than the annual mean (79± 7 min on the first and 45 ± 5 min on the second day). The maxima of the duration of action differed on the two days of the experiment. The spring maximum of duration of action of amobarbital was more marked on the first day of the experiment, the autumn maximum on the second day.

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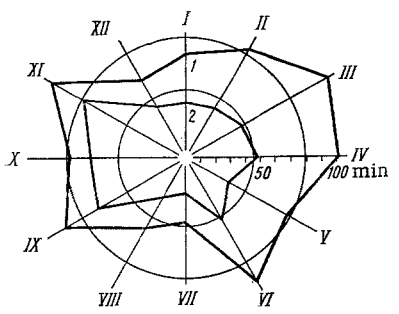

Fig. 1. Annual dynamics of mean monthly duration of action of amobarbital. Mean monthly durations of action (in min) plotted along radii. 1) Duration of action on 1st day; 2) on 2nd day of administration. Circles describe annual mean duration of action on 1st and 2nd days of experiment.

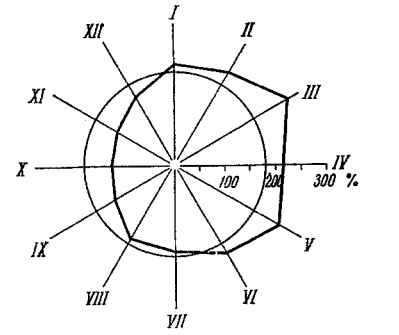

Fig. 2. Annual dynamics of production of tolerance. Monthly indices of tolerance (in %) plotted along radii. Circle describes annual mean index of tolerance.

Tolerance, expressed as the ratio (in %) between the duration of action of amobarbital on the 1st and 2nd days (the index of tolerance), is shown diagrammatically in Fig. 2. Only one cycle is shown on this diagram. Tolerance was most marked in the spring months (March, April, May) and less so in the fall (October). In some mice no tolerance whatever was observed at this time.

These results differ from those obtained by Golikov [2] in a study of seasonal variations in the duration of action of barbital sodium in mice, when only one maximum was observed (in spring). The duration of action of barbiturates is determined mainly by two factors: the sensitivity (or resistance) of the CNS to the barbiturate and the rate of its metabolism in the liver (elimination).

The results show that there is a difference between the annual cyclic change in the duration of action of amobarbital and in the degree of development of tolerance. In the former case two cycles are observed, but only one in the latter. This suggests that mechanisms with a cyclic action may influence the duration of action of the drug and also its ability to produce tolerance.

Beuthin and Bousquet [9] state that the inducing action of phenobarbital on microsomal enzymes is highest in June and lowest in October. This agrees well with the observed decrease in the development of tolerance in the fall. The reduced inducibility of the enzymes may be connected with a general (relative, perhaps) weakening of metabolism in the fall. It is well known that many metabolic processes are activated in spring (oxygen consumption [12], activity of the gonads [1]) and that the production and excretion of corticosteroids are increased in the spring [5, 6], and so on. The spring-summer functional maximum is connected with the reproductive stage of biological activity [3]. The relative weakening of metabolism ought to affect mainly the duration of action of those barbiturates which are metabolized in the body, including amobarbital. Since Golikov [2] used barbital sodium, a barbiturate which is not metabolized in the body, the delay in metabolism did not affect the drug and no second (autumnal) prolongation of its action was observed.

On the other hand, the mechanisms increasing the excitability of the CNS of mice are evidently weakened in spring, so that the duration of the hypnotic action of the barbiturate is prolonged, and the antihypnotic action of caffeine described by Golikov [2] also is weakened.

LITERATURE CITED

1. F. Beach, in: Experimental Psychology [Russian translation], Moscow (1960), p. 513.
2. P. P. Golikov, Farmakol. i Toksikol., No. 5, 540 (1966).
3. P. P. Golikov, Time of Year, Organisms, and Treatment [in Russian], Vladivostok (1968).
4. L. B. Nurmand, Farmakol. i Toksikol., No. 1, 41 (1969).
5. P. M. Torgun, Dokl. Akad. Nauk SSSR, 162, No. 5, 1205 (1965).
6. D. E. Yankelevich and M. Z. Yurchenko, Probl. Éndokrinol., No. 4, 119 (1966).
7. J. Aschoff, Z. Tierpsychol., 15, 1 (1958).
8. J. Aschoff, Ann. Rev. Physiol., 25, 581 (1963).
9. P. K. Beuthin and W. F. Bousquet, Biochem. Pharmacol., 19, 620 (1970).
10. E. Bünning, Die physiologische Uhr, Berlin (1963).
11. A. Reinberg and F. Halberg, Ann. Rev. Pharmacol., 11, 455 (1971).
12. O. Riml and H. G. Wolff, Arch. Exp. Path., Pharmak., 157, 193 (1930).
13. H. M. Webb and F. A. Brown, Physiol. Rev., 39, 127 (1959).