EFFECT OF ADRENALECTOMY ON THE TOXIC ACTION OF POISONS ADMINISTERED UNDER DIFFERENT CONDITIONS

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UDC 615.9.092:612.45-089.87

The paradoxical effect of furfural and styrene observed in intact animals (the lower mortality among the experimental animals receiving the same dose of poison by daily than by less frequent administration) is still observed in adrenalectomized mice and rats, but only until a certain stage of repeated administration of the poisons (34-38 days), after which it disappears. It is suggested that the appearance of the paradoxical effect is due to two stages in the development of adaptation reactions of the animal. The first stage is due to the activity of specific systems of poison detoxication while the second is due to the development of a general adaptation syndrome and requires the functional integrity of the pituitary – adrenal system for its adequate manifestation.

The fact that the toxic action of a poison depends not only on its does and concentration, but also on the frequency of its action, can now be taken as established.

In accordance with the views of Sarkisov [2, 4], the effect of a stimulus is determined by the relationship between the rhythm of its action and the rhythm of intracellular regeneration, and by intracellular adaptive changes.

In addition, when the action of chemical poisons is considered, the rate of their detoxication also plays an important role. The rhythm of action, leading to the development of maximal adaptive changes, is therefore different for substances which differ in their chemical nature. Examples of this are given in the literature [1]. In some cases the maximal development of adaptive changes and increased resistance to poisons arise sooner if the rhythm of action is faster. In these cases an apparently paradoxical effect arises in that the more frequent action of the poison, accompanied by administration of a much larger dose, has a less toxic action than less frequent administration of a smaller total dose of the poison. The results have been obtained in experiments with carbon tetrachloride and furfural [4].

In an investigation of this phenomenon the writers have shown [5] that it is due to the state of protein synthesis in the body. Blocking of protein synthesis by actinomycin D abolished this paradoxical effect. It was postulated on the basis of these results that each poison has its own optimal rhythm of action at which maximal development of the compensatory cellular processes takes place and the synthesis of adaptive enzymes responsible for detoxication of the poison is intensified. Meanwhile, there is plenty of evidence (summarized by Bonner [6]) to show that the synthesis of adaptive enzymes is under hormonal control. The molecular mechanism of the influence of steroid hormones on protein and enzyme synthesis in the liver has been examined [3]. There is evidently a connection between the hypothalamo–hypophyseo–adrenal system, through hormonal action on nuclear structures, with the synthesis of NADP · H_2-dependent enzyme proteins located in the microsomal fraction of the liver and responsible for detoxication of a particular poison. This hypothesis is supported by data for the catatoxic steroids, which induce NADP · H_2-dependent microsomal enzymes of the liver, destroying exogenous toxic substances [7].

(Presented by Academician of the Academy of Medical Sciences of the USSR, N. A. Kraevskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 73, No. 6, pp. 23-26, June, 1972. Original article submitted January 13, 1972.

TABLE 1. Effect of Styrene on Mortality among Adrenalectomized and Intact Albino Rats Depending on the Frequency of Its Administration

Animals	Administration of styrene	Number of animals		P
		total	dead on 35th day of experiment	
Intact	Daily	20	4	0,05
	Every 3 days	20	10	
Adrenalectomized	Daily	7	6	—
	Every 3 days	7	5	

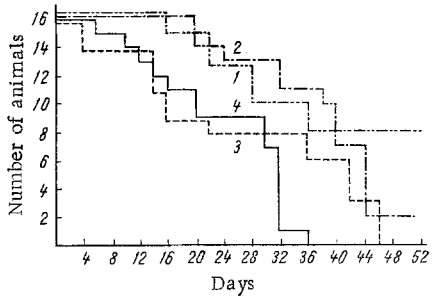

Fig. 1. Mortality of adrenalectomized and intact animals receiving furfural at different intervals: 1, 2) furfural injected into intact animals daily and on alternate days respectively; 3, 4) into adrenalectomized animals on alternate days and daily respectively.

On the other hand, it is known that the body responds by a general adaptation reaction, developing through the pituitary – adrenal system [1, 9], to unfavorable influences. The various stages of development of this reaction are connected with an increase in the nonspecific and later the specific, resistance of the body. It has also been shown that the general adaptation syndrome develops only if the action of the stressor reaches a certain intensity [8, 9]. It can accordingly be postulated that the frequent administration of a poison induces the development of a general adaptive reaction of the body. In the case of less frequent administration of the poison the general protective reaction either fails to develop at all or it develops late and the resistance of the organism to each fresh dose of poison is lowered.

If these arguments are valid the paradoxical effect must be considerably transformed in experiments on adrenalectomized animals. This hypothesis was tested in the present investigation in which repeated doses of furfural and sytrene were given.

EXPERIMENTAL METHOD

Male albino mice weighing 20-23 g, obtained from the Rappolovo nursery, were kept on a standard diet. Furfural was injected subcutaneously in a dose equivalent to 0.7 LD_{50} (200 mg/kg body weight).

The animals were divided into five groups: three groups of adrenalectomized (receiving furfural daily, on alternate days, or not at all) and two groups of intact animals, receiving furfural daily and on alternate days.

Male albino rats weighing 150-170 g were used for the experiments with styrene. They were divided into similar groups to those used in the experiments with furfural. Styrene was injected intraperitoneally in a dose of 360 mg/kg body weight daily and every 3 days.

The Student-Fisher method was used for the statistical analysis of the results.

EXPERIMENTAL RESULTS

The dynamics of the mortality after administration of furfural in identical doses, but with different frequencies of administration, to adrenalectomized and intact mice is illustrated in Fig. 1. In the groups of intact animals the paradoxical effect discovered previously was seen earlier, so that the survival rate of animals receiving furfural daily was greater than that of animals receiving the poison on alternate days [4, 5].

The adrenalectomized animals were more sensitive to the repeated injection of furfural. In both groups (administration daily and on alternate days) the animals began to die much sooner and the mortality was higher than among the intact animals. During the period of observation two of the 16 mice died in the group of adrenalectomized mice not receiving furfural.

In the adrenalectomized animals a paradoxical effect of administration of furfural also was found. Admittedly it was less marked and it showed itself only in the fact that mortality before the 30th day of the experiment was approximately equal in both groups. Meanwhile in this case also five mice died on the 29th day of the experiment after receiving the poison daily, while seven of the mice poisoned on alternate days died, despite the fact that in the first case the animals had recieved twice the total amount of poison. However, by the 36th day of the experiment all the animals in the group receiving the poison daily had died, while some of the mice receiving furfural on alternate days were still alive on the 45th day. Hence starting from the 32nd day of the experiment, the paradoxical effect disappeared in the adrenalectomized animals. The usual dependence of the effect on the total dose of the poison was established: the mortality was higher in the group receiving the poison daily.

Similar results were obtained in experiments on rats receiving styrene at different intervals. In the groups of adrenalectomized animals a paradoxical effect was observed, but to a lesser degree than in the groups of intact rats (Table 1).

Analysis of the results of these experiments suggests the following explanation. Probably at least two relatively independent systems responsible for the character of adaptation to administration of the poison at different time intervals are concerned. Initially adaptation takes place through stimulation of synthesis of protein and adaptive enzymes, i.e., the specific systems of detoxication of the poison. With respect to furfural in particular, it was only if the poison was injected daily that an increase was observed in the activity of xanthine oxidase, the enzyme responsible for conversion of aldehydes. Later, as the toxic action of the poison becomes more severe, the general adaptive system of hormonal regulation comes into operation. A general adaptation syndrome develops. By this time the specific adaptation systems are possibly exhausted, and for their work to continue, stimulation from the central components of the general adaptive system is necessary. The functional insufficiency of the pituitary-adrenal system must led in such cases to collapse of the adaptive mechanisms responsible for the paradoxical effect. Support for this hypothesis is given by disappearance of the paradoxical effect in the adrenalectomized animals at a certain stage of action of the poisons.

Two stages can thus be distinguished in the mechanism of onset and development of the paradoxical effect. Initially this effect is due to different degrees of mobilization of specific adaptive mechanisms functioning largely independently of the regulatory effect of the pituitary-adrenal system. At this stage of poisoning the effect observed is determined principally by the protective reactions of the general adaptation syndrome. These reactions are probably connected both with stimulation of specific detoxication systems and with activation of nonspecific adaptive mechanisms.

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