ON THE INFLUENCE OF APOMORPHINE ON THE TOXICITY OF ADRENALIN AND PHENAMINE

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As had been shown earlier [2], apomorphine inhibits the O-methylation of pyrocatecholamines in the organism, which evidently depends upon the inhibiting influence of apomorphine upon the activity of pyrocatechol-O-methyltransferase.

We attempted to use this action of apomorphine to clarify the question of the significance of pyrocatechol-O-methyltransferase in the inactivation of pyrocatecholamines in the central nervous system and peripheral structures of the organism. In the solution of this problem, apomorphine possesses an advantage over the inhibitors of this enzyme system usually used – pyrogallol and quercetin [3-5], in that, judging by its pronounced central action, it penetrates easily through the hematoencephalic barrier.

EXPERIMENTAL METHOD

The influence of apomorphine hydrochloride upon the toxicity of adrenalin hydrochloride and phenamine sulfate was investigated in experiments on white mice. As is well-known, lethal results under the action of toxic doses of adrenalin are explained by the peripheral action of this substance (pulmonary edema), while phenamine leads to death of the mice by acting upon the central nervous system (motor excitation, turning into clonic-tetanic convulsions). The pharmacological effects of phenamine are explained by the fact that it causes a liberation of pyrocatecholamines deposited in the tissues [6, 7].

The average lethal doses (LD_{50}) of apomorphine, adrenalin, phenamine, mixtures of apomorphine with adrenalin (one part apomorphine and three parts adrenalin, as well as three parts apomorphine and one part adrenalin), and mixtures of apomorphine with phenamine (one part apomorphine and three parts phenamine, as well as three parts apomorphine and one part phenamine), were determined with the aid of the nomographic method of probit analysis according to Litchfield and Wilcoxon [1]. All the substances and their mixtures were administered to the mice intraperitoneally.

When the effects of the two substances for which the straight lines reflecting the relationship between the logarithms of the doses and probits of the effects satisfy the criterion of parallelism are additive, the average lethal dose of a mixture of them (LD_{50_M}) can be calculated according to the formula [8];

$$\frac{1}{LD_{50_M}} = \frac{p_a}{LD_{50_a}} + \frac{p_b}{LD_{50_b}},$$

where p_a and p_b are the fractions of the components in the mixture ($p_a + p_b = 1$); LD_{50_a} and LD_{50_b} are the corresponding average lethal doses of these components.

* Deceased.

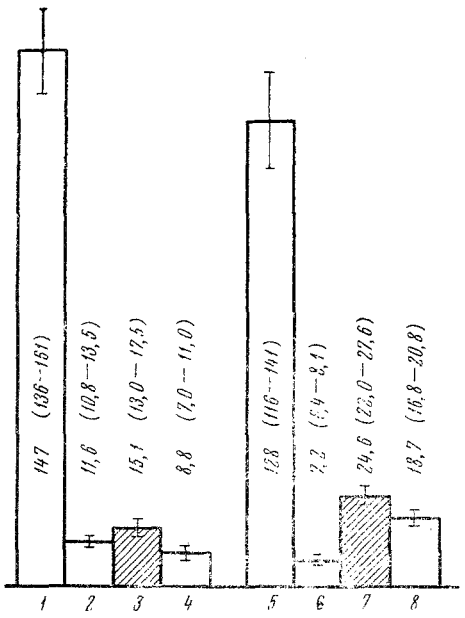

Fig. 1. Average lethal doses and their confidence limits at P = 0.05. 1) Apomorphine hydrochloride; 2) adrenalin hydrochloride; 3 and 4) mixture of adrenalin hydrochloride (three parts) with apomorphine hydrochloride (one part); 5) apomorphine hydrochloride; 6) adrenalin hydrochloride; 7 and 8) mixture of adrenalin hydrochloride (one part) with apomorphine hydrochloride (three parts). Here and in Fig. 2, the shaded columns represent the doses calculated according to the formula. Experiments on the determination of the average lethal doses of various mixtures of adrenalin with apomorphine were conducted at various times, hence each time the average lethal doses were compared for adrenalin and apomorphine.

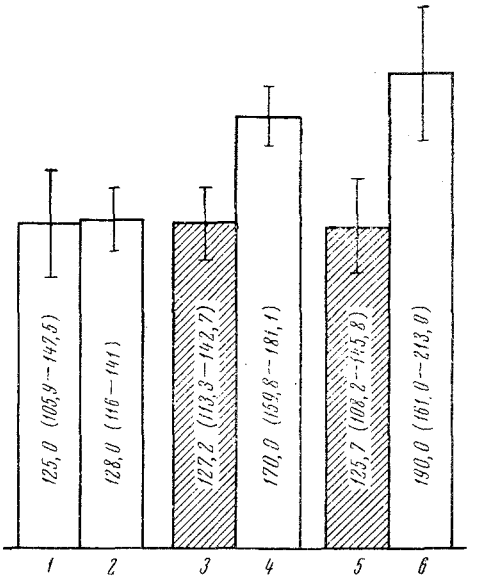

Fig. 2. Average lethal doses and their confidence limits at P = 0.05. 1) Phenamine sulfate; 2) apomorphine hydrochloride; 3) and 4) mixtures of apomorphine hydrochloride (one part) with phenamine sulfate (three parts); 5 and 6) mixture of apomorphine hydrochloride (three parts) with phenamine sulfate (one part).

RESULTS

The straight lines constructed on the basis of our experiments for apomorphine, adrenalin, and phenamine, reflecting the relationship between the logarithms of the doses of these substances and the frequencies of lethal outcomes expressed in probits, proved to satisfy the criterion of parallelism (when P equals 0.05). This permitted a comparison of the values of the average lethal doses of mixtures of apomorphine with adrenalin and apomorphine with phenamine, found by the experiments and calculated according to the formula.

As can be seen from Fig. 1, the values of the average lethal doses of mixtures of apomorphine with adrenalin, established on the basis of the experiments, proved lower than those calculated according to the formula. This difference is statistically significant ($P < 0.05$). Thus, the effect of the combined action of apomorphine with adrenalin exceeds the additive effect, which is evidence in favor of the concept of the significance of pyrocatechol-O-methyltransferase in the inactivation of adrenalin in the peripheral structures of the organism.

As for the experimentally established values of the average lethal doses for mixtures of apomorphine with phenamine, they proved to be significantly ($P \ll 0.05$) higher than those calculated according to the formula (Fig. 2). This is evidence of antagonistic relationships between these substances. However, it may be that this antagonism is not mediated through adrenergic mechanisms. Such a hypothesis is probable if we recognize a serotoninergic mechanism of the central action of phenamine [11, 12], or the fact that pyrocatechol-O-methyltransferase in the central nervous system plays no significant role in the inactivation of pyrocatecholamines [9, 10]. If the central action of phenamine is adrenergic in character and depends upon the liberation of deposited noradrenalin, and if the inactivation of the latter in the central nervous system is accomplished just as on the periphery, under the influence of pyrocatechol-O-methyltransferase, then the antagonism between apomorphine and phenamine can be explained by the fact that under the conditions of blockage of pyrocatechol-O-methyltransferase, the sorption capacity of the proteins with respect to pyrocatecholamines increases, in view of which their liberation under the influence of phenamine decreases.

SUMMARY

Experiments on albino mice were used to determine the average lethal doses of apomorphine, adrenalin, phenamine, and mixtures of apomorphine with adrenalin (1 : 3 and 3 : 1) and apomorphine with phenamine (1 : 3 and 3 : 1). The obtained values of average lethal doses for the mixtures were compared with those calculated according to these formulas: $(1/LD_{50_M}) = (p_a/LD_{50_a}) + (p_b/LD_{50b})$, where LD_{50_M} is the average lethal dose of the mixture, LD_{50_a} and LD_{50b} are the average lethal doses of its components and p_a and p_b are portions of the components in a mixture ($p_a + p_b = 1$). This formula determines the relationship between the average lethal doses of a mixture and its components in case the latter's action is additive. It was shown that the effect of the combined action of apomorphine with adrenalin was considerably in excess of the additive effect whereas the effect of the combined action of apomorphine with phenamine was significantly less than the additive effect. These results were discussed from the viewpoint of the importance of pyrocatechol-O-methyltransferase in the inactivation of pyrocatecholamines.

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