EFFECT OF BLOCKING NEURONAL AND EXTRANEURONAL UPTAKE OF BIOAMINES ON THE ADRENOSENSITIZING ACTION OF TRICYCLIC ANTIDEPRESSANTS

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Experiments on isolated intact, and also denervated, vasa deferentia of rats showed that tricyclic antidepressants (melipramine,* noveril,† azaphen), in low concentrations ($1 \cdot 10^{-9}$ g/ml), like cocaine ($1 \cdot 10^{-5}$ g/ml), have an aminopotentiating action. Denervation followed by blocking of extraneuronal uptake of the amine by deoxycorticosterone ($1 \cdot 10^{-5}$ g/ml) did not change the position, shape, or slope of the concentration–effect curves of noradrenalin obtained in the presence of noveril and cocaine. It is postulated that the mechanism of the adrenosensitizing action of tricyclic antidepressants on smooth-muscle organs is predominantly postsynaptic.

KEY WORDS: smooth muscles; neuronal and extraneuronal uptake of bioamines; denervation; antidepressants.

Imipramine-like antidepressants, like cocaine, potentiate the central and peripheral effects of noradrenalin [3, 4, 12]. However, the intimate mechanism of the adrenosensitizing action of the tricyclic antidepressants remains unexplained. Some workers [1, 8, 13] consider that the aminopotentiating action of the antidepressants is the result of cocaine-like inhibition of reassimilation of bioamines, whereas others [5, 6, 14, 15] regard this phenomenon as postsynaptic in nature.

Results obtained on the rat vas deferens served to clarify existing views on the nature of the adrenosensitizing action of imipramine-like antidepressants on smooth-muscle organs.

EXPERIMENTAL METHOD

Experiments were carried out on isolated intact vasa deferentia of rats and also the same organs when denervated by Shibata's method [11], kept in a bath with Krebs' solution (37°C), aerated with oxygen. The cumulative curve method [9] was used to study how the effects depended on the noradrenalin concentration. Points on the concentration–effect curve were determined by averaging the results of experiments on six to eight vasa deferentia. The concentration–effect curves of noradrenalin were found before and after treatment of the preparation for 20 min with the antidepressant in a concentration of $1 \cdot 10^{-9}$ g/ml.

Of the tricyclic antidepressants, melipramine, noveril, and azaphen were investigated; their adrenosensitizing effect was compared with the corresponding action of cocaine, used in a concentration of $1 \cdot 10^{-9}$ g/ml and $1 \cdot 10^{-9}$ g/ml.

In the other series the experiments were carried out on isolated denervated vasa diferentia of rats followed by blocking extraneuronal uptake of bioamines, produced by treatment of the vasa for 30 min with a solution of deoxycorticosterone [7, 10] in a concentration of $1 \cdot 10^{-5}$ g/ml.

The degree of denervation was determined by a histofluorescence method and also from the absence of a contractile response to tryamine in a concentration of $1 \cdot 10^{-3}$ g/ml.

*Imipramine – Translator.
† Dibenzepine hydrochloride – Translator.

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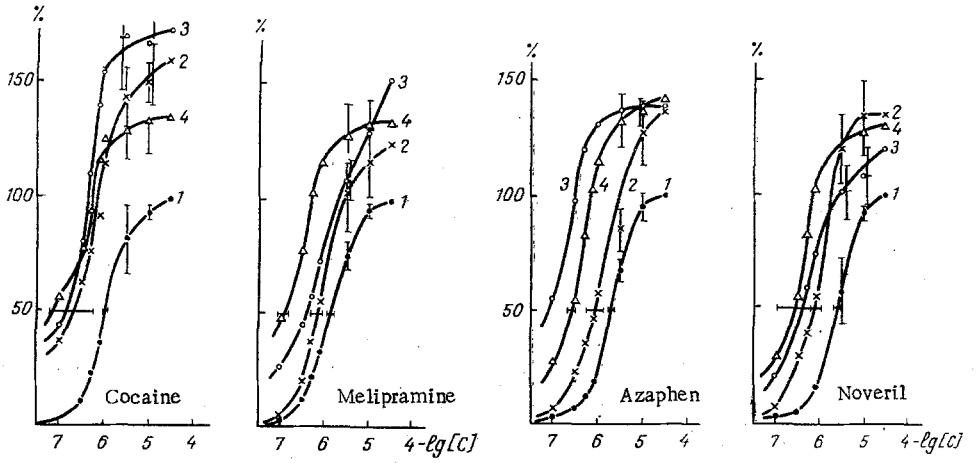

Fig. 1. Cumulative concentration–effect curves for noradrenalin obtained on isolated rat vasa deferentia before and after treatment with antidepressant or cocaine: 1) native preparations (control); 2) native preparations after preliminary treatment with antidepressant or cocaine; 3) denervated preparations after preliminary treatment with antidepressant or cocaine; 4) denervated preparations with subsequent blocking of extraneuronal uptake of amines after preliminary treatment with antidepressant or cocaine. Abscissa, negative logarithms of concentrations; ordinate, effect (in % of maximal).

EXPERIMENTAL RESULTS

Preliminary treatment with the antidepressant significantly affected the character of the curves of contractile effect versus noradrenalin concentration (Fig. 1).

The adrenosensitizing effect of cocaine ($1 \cdot 10^{-5}$ g/ml) and the imipramine-like antidepressants, used in a concentration of $1 \cdot 10^{-9}$ g/ml, was manifested not only as a shift of the concentration–effect curve to the left, but also as a marked increase in the maximum of the contractions of the native vasa induced by noradrenalin. Preliminary treatment for 20 min with the antidepressant (or cocaine) of the denervated vasa deferentia had an adrenopotentiating action; the curves showing the contractile effect as a function of bioamine concentration obtained in this case, moreover, did not differ significantly from the curves obtained with the native preparations. The logarithm of concentration versus effect of noradrenalin curves obtained in the presence of noveril and cocaine on denervated vasa deferentia treated with deoxycorticosterone in order to block extraneuronal uptake of the amine did not differ significantly in shape, position, or slope from the curves obtained on denervated and native ducts. The curves obtained under similar conditions in the presence of melipramine and azaphen were shifted to the left along the concentration scale by a greater degree than the curves obtained on native or purely denervated vasa.

The adrenopositive action of cocaine and noveril, as exhibited on the vas deferens, cannot thus be explained by their ability to inhibit the reassimilation of bioamines by endings of adrenergic fibers and by muscle tissue. The adrenosensitizing action of these drugs is evidently effected at the level of the postsynaptic membrane, and their action may take place by the principle of allosteric sensitization [2] of the adrenergic receptors or at the level of "transreceptor" mechanisms. The adrenosensitizing effect of melipramine and azaphen is due not only to their influence at the postsynaptic level, but also to the inhibition of the tissue uptake.

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EFFECT OF ETHYRAZOLE AND PARMIDINE ON THE DEVELOPMENT OF EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS

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In rabbits receiving cholesterol with the diet for 3-4 months the accumulation of total cholesterol in the aorta and the degree of severity of atherosclerosis of the aorta were reduced by administration of ethyrazole and parmidine. These substances had no substantial effect on the blood cholesterol, triglyceride, and phospholipid levels of these animals.

KEY WORDS: aorta; lipids; atherosclerosis.

Previous investigations have shown that the compound ethyrazole (bis-methylamide-1-ethylpyrazole-3,4-dicarboxylic acid) has a marked antiinflammatory action [4]. A similar property is found in the structurally closely related compound pyridinol carbamate (bis-N-methylcarbamino ester of 2,6-bis-hydroxymethylpyridine) [7, 11], which has been used with success for the prevention and treatment of atherosclerosis and ischemic heart disease [8, 12].

Considering the role of changes in the blood vessel wall in the pathogenesis of atherosclerosis [9, 12] and also data showing the ability of pyridinol carbamate to prevent the penetration of atherogenic lipoproteins into the arterial wall [12], an investigation was carried out to compare the effect of ethyrazole and parmidine, a Soviet preparation of pyridinol carbamate synthesized at the All-Union Pharmaceutical Chemical Research Institute, on lipid metabolism and experimental atherosclerosis in rabbits.

EXPERIMENTAL METHOD

In experiments with ethyrazole, male rabbits (2.3-2.7 kg) were given cholesterol (0.3 g/kg) and the compound (30 mg/kg) with the diet for 3 months, and in the experiments with parmidine the rabbits received cholesterol (0.25 mg/kg) and the compounds (10 mg/kg) for 4 months. Animals of the control groups received cholesterol alone in the above amounts. The blood serum levels of total cholesterol [6], triglycerides [10], phospholipids [13], and total lipids [14] were determined. The animals were killed by injection of air into the auricular vein, the aorta was removed along its whole length, measured by planimetry [1], and its total cholesterol content was determined. The content of cholesterol and total lipids in the liver was determined. In the rabbits receiving cholesterol alone or cholesterol with parmidine the aorta also was investigated morphologically, with quantitative estimation of lipids in individual plaques in different parts of the aorta, using the stereological principle [3, 5]. The numerical results were subjected to statistical analysis [2].

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