THE USE OF FTORACIZINE TO PREVENT EXHAUSTION OF THE CATECHOLAMINE RESERVES BY RESERPINE

V. A. Arefolov, L. V. Panasyuk, and K. S. Raevskii

UDC 612.452.018.014.46: [615.214.22+615.214.32

The content and distribution of catecholamines in terminal fibers of the dura mater of rats after administration of reserpine, of the new antidepressant ftoracizine, and a combination of both drugs were studied by the method of histochemical fluorescence of biogenic amines. The results showed that ftoracizine does not reduce the reserves of the adrenergic mediator but has the ability to prevent exhaustion of those reserves by reserpine.

Investigations have shown that the new antidepressant ftoracizine [10-(b-diethylaminopropionyl)-2-trifluoromethylphenothiazine hydrochloride], like other tricyclic thymoleptics, has a marked antireserpine action [1, 2]. The suggestion has been made that the adrenergic mediator plays a role in the mechanism of the antagonism between antidepressants and reserpine [5, 7].

It was therefore decided to study the action of ftoracizine from this standpoint and, in particular, to determine whether it has any effect on the reserves of the adrenergic mediator of the nervous system or on their exhaustion by reserpine.

EXPERIMENTAL METHOD

Adrenergic nerve fibers of the dura mater of rats weighing 180-220 g were used as the test objects. Reserves of the adrenergic mediator in the fibers were studied by the histochemical method of fluorescence of the catecholamines using a modified Falck's method [4] for film preparations. In the experiments of series I ftoracizine was injected in doses of 10 and 20 mg/kg and the animals were sacrificed 1, 2, and 3 h later. In series II the rats were decapitated 15 and 30 min and 1, 2, 3, and 4 h after injection of reserpine in doses of 1 and 2.5 mg/kg. In series III, 1 and 2 h after injection of ftoracizine in the above-mentioned doses, the animals received reserpine in doses of 1 and 2.5 mg/kg. The rats were decapitated 3 h after injection of reserpine. In all experiments the substances were injected intraperitoneally.

EXPERIMENTAL RESULTS

In the control animals adrenergic fibers treated by Falck's method [4] gave the typical specific green fluorescence, with the formation of a dense network of terminal fibers, anastomosing with nerve filaments in the vessel walls (Fig. 1A). Along their length the terminal fibers contained brightly luminescent varicosities, joined together by segments with weaker fluorescence.

The pattern of fluorescence 1, 2, and 3 h after injection of ftoracizine in doses of 10 and 20 mg/kg was indistinguishable from normal (Fig. 1B). This is evidence that ftoracizine does not produce exhaustion of the reserves of adrenergic mediator detectable by the histochemical fluorescence method.

After injection of reserpine the changes in the pattern of fluorescence varied from almost imperceptible to the almost total disappearance of the specific fluorescence of the adrenergic fibers (Fig. 2A). The

Electron Microscopy Group, Laboratory of Pharmacology of the Nervous System, Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 74, No. 10, pp. 48-51, October, 1972. Original article submitted March 8, 1972.

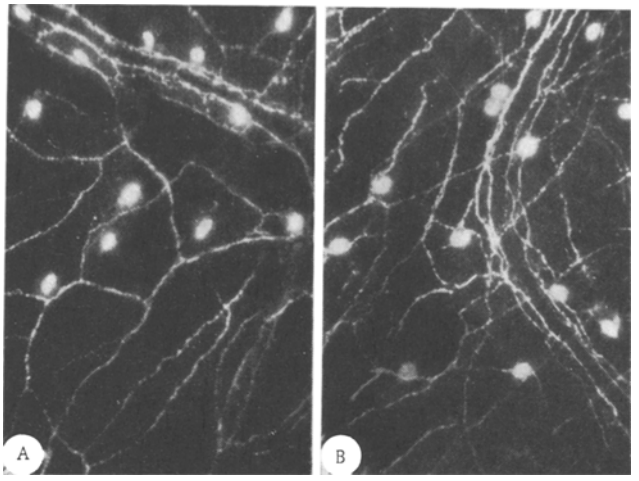

Fig. 1. Fluorescence of adrenergic mediator in fibers of dura mater of rat in control series (A) and after administration of ftoracizine (B), 120 ×.

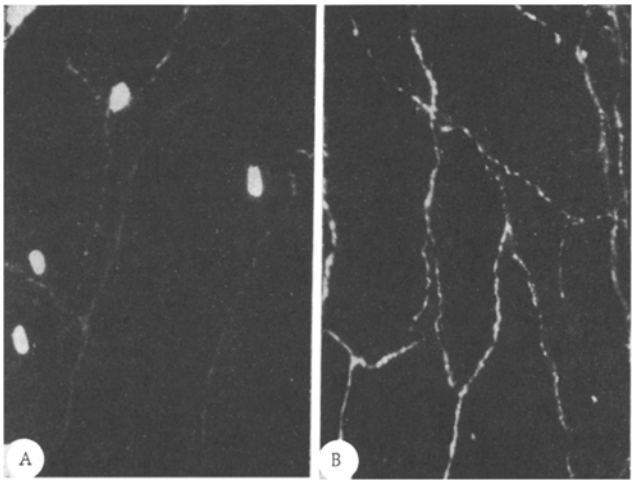

Fig. 2. Fluorescence of adrenergic mediator in fibers of dura mater of rat after injection of reserpine and a combination of ftoracizine with reserpine: A) 3 h after injection of 1 mg/kg reserpine (180 ×); B) 2 h after injection of 20 mg/kg ftoracizine followed by injection of 1 mg/kg reserpine (150×).

results depended on the dose and, in particular, on the time of injection of the drug, although the sequence of the changes was nearly always the same. For instance, 15 min after injection of reserpine in a dose of 2.5 mg/kg the pattern of fluorescence was virtually indistinguishable from that in the control. After 30 min the first slight changes were seen in the brightness of fluorescence and in the density of distribution of the fibers: among the brightly fluorescent plexus of nerves appeared small "islands" – areas of fibers with only moderate fluorescence. In these areas 1 and 2 h after injection of the neuroleptic the fluorescence was weak and hard to distinguish. In the terminal fibers which remained intact, some decrease in the brightness of fluorescence was observed, whereas the nerves of the blood vessels were changed to a lesser degree. Many of the remaining fibers 3 h after injection gave off a weak fluorescence, the number of fibers in the vessel walls was appreciably reduced, but they still continued to fluoresce. A marked decrease in the intensity of fluorescence of the terminals was observed 4 h after injection of the drug.

When reserpine was given in a dose of 1 mg/kg the character of the histochemical changes was similar in direction as when the larger dose was given. For instance, 3 h after injection of reserpine in a

dose of 1 mg/kg, weak fluorescence was observed in the terminal fibers, although in some cases moderate fluorescence of the varicosities still remained (Fig. 2B).

In the next series of experiments ftoracizine was given 30 min and 1 and 2 h before reserpine. Three hours after injection of reserpine when, judging from the results described above, the effect of exhaustion of the mediator was clearly defined but had not yet reached its maximum, the animals were decapitated. It was found that when ftoracizine, in a dose of 20 mg/kg, was injected 1 or 2 h before reserpine the brightness of fluorescence and the density of the network of nerve fibers were greater than in the experiment with reserpine alone (Fig. 2B). After a smaller dose of ftoracizine (10 mg/kg) the picture of fluorescence was virtually the same as in the experiment with reserpine. It will be noted that no decrease in the effect of reserpine likewise was found if ftoracizine was injected 30 min before the reserpine. The preventive effect was manifested more clearly if the reserpine was injected in a smaller dose (1 mg/kg).

The inhibition of fluorescence of the adrenergic nerves observed after injection of reserpine is the result of exhaustion of the reserves of mediator in the terminal nerve branches of the dura mater, as has been shown for nerves of other tissues, especially the iris [6].

Presumably ftoracizine prevents the exhaustion of reserves of adrenergic mediator induced by reserpine in several different ways: a) by interfering with the liberation of mediator from its reserves in the nerve fibers, and b) by blocking penetration of reserpine through the axon membrane to the reserves of the mediator. In the latter case, a unique type of competition may take place for the sites of penetration of the substances through the neuronal membrane. Another possible explanation is that both these mechanisms operate simultaneously.

Similar views have been expressed with regard to the antagonism of bretylium and cocaine with reserpine [3].

LITERATURE CITED

1. Yu. I. Vikhlyaev, G. Ya. Avrutskii, S. V. Zhuravlev, et al., in: Current Problems in Psychopharmacology [in Russian], Kemerovo (1970), p. 271.
2. A. N. Gritsenko, Z. I. Ermakova, S. V. Zhuravlev, et al., Khim.-Farmats, Zh., No. 6, 18 (1971).
3. B. A. Gallingham and R. Cass, J. Pharm. (London), 14, 385 (1962).
4. B. Falck and C. Owman, Acta Univ. Lund, Section 2, No. 7, Lund (1965), p. 8.
5. F. Garattini, A. Giachetti, A. Jori, et al., Acta Univ. Lund., Section 2, No. 7, Lund (1965), p. 509.
6. T. Malmfors, Acta Physiol. Scand., 64 (1965).
7. F. Sulser and F. Soroco, Psychopharmacologia (Berlin), 8, 191 (1965).