EFFECT OF FLUACIZINE ON THE UPTAKE OF EXOGENOUS NORADRENALIN BY THE ISOLATED RAT VAS DEFERENS

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The contractile power of the rat vas deferens and the content of adrenergic neurotransmitter in it during incubation of the vas in medium with exogenous noradranelin (NA) or with the new antidepressant fluacizine and NA, were studied by transmural electrical stimulation and spectrofluorimetry. Addition of NA to the medium led to tonic contraction of the vas (contracture), to a very small increase in the response to the electric pulse, and to an increase in the content of neurotransmitter in the tissue. Incubation of the vas in medium containing fluacizine and NA was followed by an even stronger contracture of the vas despite no increase in the NA concentration in the organ. The effects observed are attributed to blocking of the uptake of exogenous NA by the tissue of the vas by fluacizine.

Antidepressants of the imipramine group have the property of preventing the accumulation of exogeneous nonadrenalin (NA) by adrenergic nerve endings [5, 8] and of strengthening the contraction of adrenergically innervated smooth-muscle organs in response to electrical stimulation and after incubation with NA [1].

It was decided to study the new phenothiazine antidepressant fluacizine [10-(β-diethylaminopropionyl)-2-trifluoromethyl-phenothiazine hydrochloride] from this standpoint.

EXPERIMENTAL METHOD

Experiments were carried out on male rats weighing 180-280 g. The vas deferens was isolated from the animals after decapitation and placed in oxygenated Krebs' solution at 32°C. In the experiments of group 1 the NA concentration in the tissues of the vas was determined after incubation for 45 min. The degree of accumulation was estimated from the increase in NA content in the tissues of the vas after incubation for 30 min with NA solution (0.5 μg/ml). In some experiments the organ was first incubated with fluacizine (in concentrations of 1, 5, and 10 μg/ml) for 15 min, after which the medium was replaced by a solution containing fluacizine in the same concentration and NA (0.5 μg/ml).

The NA concentration was determined by the method of Euler and Lishajko [6], and the fluorescence of the solutions was recorded with the "Opton" spectrofluorimeter at wavelengths of 395 and 505 mm. The NA content was expressed in μg/g wet weight of tissue or as percentages of the control.

In the experiments of group 2 the contractile power of the vas was studied in response to transmural electrical stimulation, after which, as in group 1, the NA content in the vas was determined. Stimulation (square pulses, 0.1 msec, 100 V, 30 Hz, 3 sec) was applied by platinum ring electrodes [1] every 2 min. Contractions of the vas were recorded with an automatic writer. Changes in the amplitude and initial level of the contractions were expressed as percentages of the control. Stable contractions of constant amplitude

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TABLE 1. Effect of Fluacizine on Uptake of Exogenous NA by the Rat Vas Deferens in Vitro

Substance and concentration	Sequence and time of incubation (in min)				NA concentration	
	Krebs' solution	fluacizine	NA	fluacizine+NA	μg/g wet wt. of tissue	% of control
Control	45	—	—	—	17,2±2,3**	100
Exogenous NA (0,5 μg/ml)	15	—	30	—	21,6±1,7	126
Fluacizine (1 μg/ml) and NA*	—	15	—	30	16,3±1,2	95
Fluacizine (5 μg/ml) and NA*	—	15	—	30	16,0±2,5	93
Fluacizine (10 μg/ml) and NA*	—	15	—	30	16,8±1,9	98

*NA concentration in incubation medium in these series of experiments was 0.5 μg/ml.
†Confidence limits of the means for P = 0.05.

TABLE 2. Effect of Fluacizine on NA Concentration and Contractile Power of the Rat Vas Deferens Incubated with Exogeneous Noradranalin

Substance and concentration	Sequence of time of incubation (in min)				NA concentration		Mean contracture and mean amplitude of contractions in 30 min (in % of control)	
	Krebs' solution	fluacizine	NA	fluacizine+NA	μg/g wet weight of tissue	% of control	contracture	amplitude
Control	45	—	—	—	9,5±0,7*	100	—	100±10*
NA (0.5 μg/ml)	30	—	15	—	12,4±2,8	130	—	—
Fluacizine (1 μg/ml) and NA (0.5 μg/ml)	15	—	30	—	14,2±2,6	149	13±4	106±9
	15	15	—	15	9,8±2,2	103	—	—
	—	15	—	30	9,3±2,0	98	71±15	82±13

*Confidence limits of the means for P = 0.05.

were obtained 1.5 h after the beginning of incubation. The subsequent procedures were the same as in the experiments of group 1. The duration of incubation was 15 and 30 min.

The following substances were used in the experiments: noradranalin hydrotartrate (Khar'kov Endocrine Preparations Factory) and fluacizine (Institute of Pharmacology, Academy of Medical Sciences of the USSR).

EXPERIMENTAL RESULTS

The results in Table 1 show that the mean NA content in the tissue of the vas during incubation for 45 min was 17.2 μg/g. Incubation with the addition of NA to the medium led to a statistically significant increase in the NA concentration in the tissue by 26% ($P < 0.05$). In the experiments in which the vas was incubated in medium containing fluacizine as well as NA, no increase occurred in the NA content. Increasing the concentration of antidepressant in the medium to 5 and 10 μg/ml did not change this effect.

The results of the experiments of group 2, summarized in Table 2, indicate that after a more prolonged preliminary incubation of the organs and after their electrical stimulation the total NA level in the tissue fell to 9.5 μg/g tissue. The addition of NA to the medium in a concentration of 0.5 μg/ml led to an increase in the concentration of the neurotransmitter just as in the experiments of group 1. The NA level 15 min after its addition did not yet significantly differ from the control (there was only a tendency for it to

increase), but 30 min after its addition it was significantly increased (by 49%). Fluacizine completely abolished the accumulation of exogenous NA.

The study of the contractile power of the vas deferens during transmural stimulation showed that stable contractions persisted unchanged throughout the period of investigation. The addition of NA (0.5 μg · ml) to the medium led in every case to the appearance of tonic contraction of the vas (contracture), as reflected in a mean increase of 13% in the initial level for a 30-min period of incubation and a very slight increase in amplitude of the contractions in response to electrical stimulation. Incubation of the vas with fluacizine and NA was followed by an even more marked and prolonged contracture of the organ than in the experiment with NA alone, although the response to electrical stimulation was not increased. The results of calculation of the mean contracture of the vas and the mean amplitude of the contractions over a period of 30 min, expressed as percentages of the contractions in the control, are given in Table 2.

The increase in the NA concentration after incubation of the vas deferens with exogenous NA can be regarded as the result of active uptake of the neurotransmitter by terminal adrenergic nerve fibers, as has been demonstrated experimentally [9, 10]. After incubation with fluacizine no increase was found in the NA concentration; this evidently indicates that fluacizine has the ability to prevent the uptake and accumulation of exogenous NA by the tissue. Tricyclic antidepressants of the imipramine group are known to have a similar property [5, 8]. Fluacizine may perhaps act in a similar way.

Potentiation by fluacizine of the tonic contracture of the vas deferens evoked by NA, observed in the experiments, can also be explained by the ability of fluacizine to block the uptake of NA by the tissue; during incubation with exogeneous NA this could be accompanied by a considerable increase in the concentration of the neurotransmitter in the receptors. Imipramine and other antidepressants are known to have similar properties [1, 7].

The results of this investigation, in conjunction with those of the writers' earlier experiments [2, 3], demonstrate the considerable similarity of fluacizine with the other tricyclic antidepressants, in agreement with the results of the pharmacological study of fluacizine [4].

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