PROPERTIES OF SEROTONIN-SENSITIVE STRUCTURES OF THE RIGHT ATRIUM IN RABBITS

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The action of serotonin on the isolated right atrium of rabbits is shown to be not myotropic, but mediated through β-adrenergic structures. Serotonin-sensitive structures of the rabbit right atrium differ from known M-serotonin-sensitive structures and possess high sensitivity and selectivity of action relative to antagonists of the T-type. These structures can therefore be regarded as T-serotonin-sensitive in character.

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According to Trendelenburg [8], the positive inotropic effect of serotonin on the isolated right atrium of rabbits is not the result of its direct myotropic action, but is due to liberation of catecholamines. This effect may be due to the action of serotonin on intramural nervous structures. In the modern view, serotonin-sensitive structures of peripheral nerve tissue are divided into two types: structures of autonomic ganglia (M-type) and structures belonging to the afferent component of the cardio-pulmonary reflexogenic zone (T-type) [1, 2, 5, 6, 8, 9].

The object of the present investigation was to determine to which of these two types the structures of the rabbit right atrium belongs.

EXPERIMENTAL METHOD

The isolated right rabbit atrium was placed in oxygenated Locke's solution at 30° C [8]. The amplitude of the cardiac contractions was recorded mechanographically. To test the contractile power of the atrium and the specificity of action of the antagonists, control tests to adrenalin and noradrenalin were carried out at the beginning and end of each experiment. The drugs were added to the nutrient solution (25 ml) in a dose of 0.1-0.5 ml of the aqueous solution: Stimulants at intervals of 20-30 min, blocking agents 5 min before addition of the stimulants (10 min before in the case of inderal). The background was restored by changing the solutions (with 5 times their volume of Locke's solution).

In cases when the results were subjected to statistical analysis, the positive inotropic effect was calculated as a percentage of the maximum contraction measured in millimeters, deducting the spontaneous background contraction. The mean effective dose (ED_{50}) with confidence limits was determined graphically. The type to which the serotonin-sensitive structures of the rabbit right atrium belong was determined from the effects of serotonin agonists and antagonists, for besides their morphological characteristics (smooth-muscle, ganglionic, and receptor-afferent components of the reflex), serotonin-sensitive structures have well-marked pharmacological characteristics, enabling structures of D-, M-, and T-types to be distinguished.

The following compounds were used for this purpose: Phenyldiguanide (a serotonin synergist in its neurotropic effect, and not possessing a myotropic action), phentolamine and inderal (to estimate the indirect action of serotonin through adrenergic structures), morphine, tipindole [dimethylaminoethyl ester of 1, 3, 4, 5-tetrahydrothiopyrano(4, 3-β-indole-8-carboxylic acid], and six other derivatives of 2, 3-dialkylindole, tetrahydrocarbazole, tetrahydrocarboline, and tetrahydrothiopyranoindole, procaine, lignocaine, trimecaine (to determine whether the structures studied belong to the M- or T-type), serotonin creatinine sulfate, l-noradrenalin bitartrate, and adrenalin hydrotartrate.

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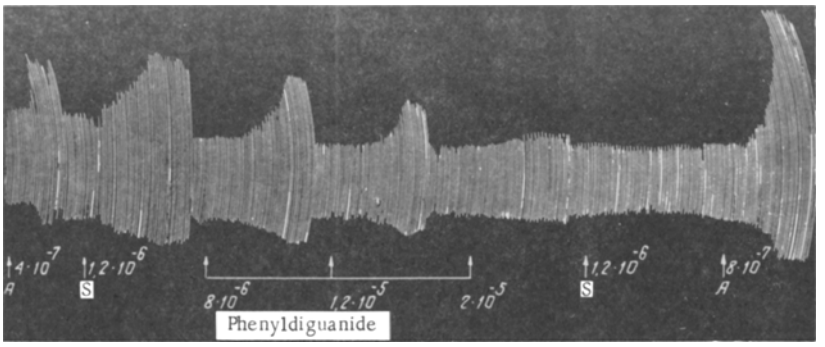


Fig. 1. Effect of phenyldiguanide on isolated right atrium of a rabbit: A) adrenalin; S) serotonin (concentrations given in g/ml).

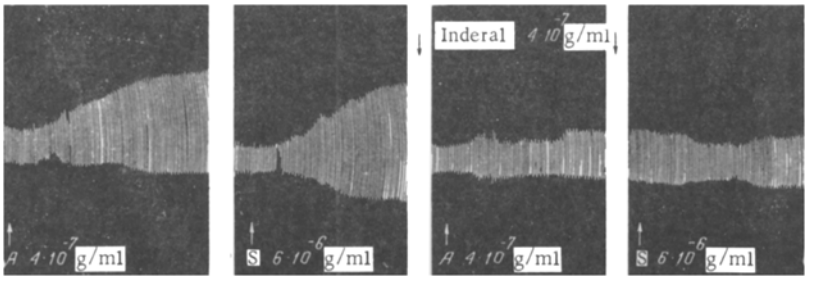


Fig. 2. Effect of inderal on positive inotropic effects of adrenalin and serotonin: A) adrenalin; S) serotonin.

EXPERIMENTAL RESULTS AND DISCUSSION

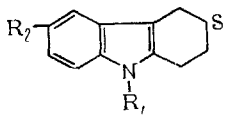
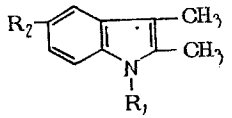
The investigations showed that phenyldiguanide, like serotonin, produces a positive inotropic effect starting with concentrations of $1 \cdot 10^{-6}$ g/ml upward. When reactions were obtained to increasing concentrations of phenyldiguanide, the effect increased up to a certain limit. A further increase in concentration lead to a decrease in the positive inotropic effect. After high concentrations the atrium ceased to respond either to phenyldiguanide or to serotonin, but continued to respond to adrenalin (Fig. 1). The crossed tachyphylaxis suggests that both antagonists act upon the same reactive structure, and coincidence between the doses of phenyldiguanide and serotonin suggests that the action of serotonin is not myotropic, but is evidently neurotropic.

The α-adrenergic blocking agent phentolamine, in a concentration of $2 \cdot 10^{-5}$ g/ml, depressed the reaction to serotonin by 78% but did not affect the reaction to noradrenalin. Meanwhile, the β-adrenergic blocking agent inderal began to show its effect in concentrations of $4 \cdot 10^{-7}$ g/ml. In this concentration inderal considerably inhibited or completely abolished effects both to adrenalin and to serotin (Fig. 2). This fact shows that the action of serotonin is mediated through β-adrenergic structures.

Morphine began to act on the rabbit atrium in a concentration of $1 \cdot 10^{-5}$ g/ml. In concentrations of $4 \cdot 10^{-5}$–$6 \cdot 10^{-5}$ g/ml it shifted the dose-effect curves of serotonin to the right along the abscissa parallel to the standard curve after the effect had reached its maximum; the background was restored rapidly. However, despite the fact that the dose-effect curve against the background of morphine was of the competitive type, the serotonin-sensitive structures of the rabbit atrium differ from M- structures because morphine blocks ganglionic effects of serotonin in concentrations of $1 \cdot 10^{-9}$ g/ml [7]. Moreover, no histological confirmation of a sympathetic ganglionic relay has been found in the right atrium of the rabbit [4]. Tipindole, on the other hand, began to act in concentrations of $1 \cdot 10^{-9}$–$1 \cdot 10^{-8}$ g/ml. A complete block was obtained in concentrations of $4 \cdot 10^{-7}$ g/ml or more.

The effect of tipindole on the rabbit atrium was prolonged and was not associated with an adrenolytic or sympatholytic action: the effects of adrenalin and noradrenalin were not inhibited by tipindole, even when the concentration of the latter was increased by 10-100 times.

TABLE 1. Effect of Indole Derivatives on Serotonin Effects

Identification No.	Compounds†			Isolated right atrium of rabbit		Relative antiserotonin activity of compounds studied on structures of D-, M-, and T-types*		
	general formula	R_1	R_2	ED_{50} (in moles/ml)	relative activity	D	M	T
K-195 tipindole		H	—COO $(CH_2)_2N(CH_3)_2$	$2,6\cdot10^{-7}$ ($8,5\cdot10^{-8}$—$7,8\cdot10^{-7}$)	1	1	1	1
K-191		H	NH_2	$1,7\cdot10^{-4}$ ($9,8\cdot10^{-5}$—$2,7\cdot10^{-4}$)	0,004	0,41	0,09	Less than 0,1
K-277		CH_3	—COO $(CH_2)_2N(CH_3)_2$	$4\cdot10^{-5}$ ($2,7\cdot10^{-5}$—$5,5\cdot10^{-5}$)	0,007	1,44	19,3	0,12
K-280		$(CH_2)_2$ N	—COO $(CH_2)_2N(CH_3)_2$	$3\cdot10^{-5}$ ($2,4\cdot10^{-5}$—$3,9\cdot10^{-5}$)	0,01	0,69	0,35	Less than 0,1
ALA-251		$(CH_3)_2$ H	—COO $(CH_2)_2N(CH_3)_2$	$3,9\cdot10^{-7}$ ($2,3\cdot10^{-7}$)	0,8	1,89	4,4	0,75
K-281 indocarb				$1,57\cdot10^{-5}$ ($1,2\cdot10^{-5}$—$2\cdot10^{-5}$)	0,02	83,3	5,5	0,65
ALA-306 diamind				$9,3\cdot10^{-6}$ ($4,4\cdot10^{-6}$—$1,9\cdot10^{-5}$)	0,04	196	0,23	0,13

*Studied by I. N. Pidevich, Z. P. Senova, and I. B. Fedorova.

*Synthesized by N. F. Kucherova, L. A. Aksanova, and L. M. Sharkova.

The suggestion that the structures studied belong to the T-type was also confirmed by the results of tests of six indole derivatives similar in their chemical structure to tipindole, but differing in the selectivity of their antiserotonin activity on structures of D-, M-, and T-types (Table 1). The results given in this table show that serotonin-sensitive structures of the rabbit atrium more closely resemble structures of the T-type in their sensitivity to the blocking effects of the tested group of indoles. Further confirmation has been obtained from investigations with anesthetics [3]. According to Gilev and Pidevich [1, 2], procaine has a depriming effect on T-structures. More powerful local anesthetics (lignocaine and trimecaine), on the other hand, do not inhibit chemoreflexes [1, 2, 3]. The same relationship was observed on the rabbit atrium.

This investigation thus showed that the action of serotonin is not myotropic but is mediated through β-adrenergic structures. Evidence of this was given by the experiments with phenyldiguanide, phentolamine, and inderal. These results are in agreement with those obtained by Trendelenburg [8], who showed that LSD-25, in doses blocking smooth-muscle structures, does not abolish the inotropic effect of serotonin. In doses 10-100 times larger, its action is nonspecific. The effects of nicotine and serotonin in reserpinized animals were almost completely abolished. Xylocholine abolishes the action of serotonin and nicotine but does not affect the response to exogenous noradrenalin.

The present investigations also showed that serotonin-sensitive structures of the rabbit right atrium differ from known serotonin-sensitive structures of the M-type and possess high sensitivity and selectivity of action relative to antagonists of the T-type.

To study the problem of what unites the studied serotonin-sensitive structures and which of them are responsible for production of the Bezold–Jarisch effect, further investigations are needed.

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