ROLE OF SULFHYDRYL GROUPS IN THE MECHANISM OF UTERINE CONTRACTION IN RESPONSE TO STIMULATION OF CHOLINERGIC AND SEROTONINERGIC RECEPTORS

M. L. Tarakhovskii

UDC 612.627.014.46:547.269.1

Experiments on the isolated uterine cornu of noninbred albino rats showed that blocking SH-groups with cadmium sulfate inhibits spontaneous contractile function of the uterus and its response to injection of aceclidine and serotonin. The stimulant action of barium chloride continued unchanged under these conditions. Unithiol restores the spontaneous contractile function of the uterus but does not restore its response to aceclidine and serotonin. The results point to an important role of sulfhydryl groups in the mechanism of uterine contraction in response to stimulation of cholinergic and serotoninergic receptors.

The presence of SH groups in the protein molecules of cholinergic and adrenergic receptors and the participation of these groups in interaction of the receptor structures of the cell with various sympatho- and parasympathotropic drugs have been established experimentally [1-3, 5, 7-10, 13-15]. Meanwhile the role of the SH groups of the protein structures of the myometrium during the action of various drugs on the uterus has been inadequately investigated. Unithiol abolishes the blocking action of cadmium on the uterine muscle of rabbits [16]. In the presence of mercuric chloride the effect of noradrenalin on the rat uterus is not inhibited [5]. The writer's previous experiments [11, 12] demonstrated the role of the SH groups of cholinergic receptors in the mechanism of stimulation of the uterus by neostigmine.

This paper describes data on the role of SH groups during interaction of aceclidine and serotonin with cholinergic and serotoninergic receptors of the uterus respectively.

EXPERIMENTAL METHOD

Experiments were carried out on the isolated uterine cornu of noninbred albino rats weighing 180-250 g. The uterine cornu was placed in Kravkov's solution at 38°C through which oxygen was bubbled continuously. SH groups were blocked with cadmium sulfate in dilutions of $1 \cdot 10^{-5} - 2 \cdot 10^{-5}$. The substances for testing were used in the following dilutions: aceclidine $4 \cdot 10^{-5}$, serotonin $4 \cdot 10^{-6}$, unithiol $1 \cdot 10^{-3}$–$2 \cdot 10^{-6}$, barium chloride $2 \cdot 10^{-4} - 4 \cdot 10^{-4}$, morphine hydrochloride $1 \cdot 10^{-5}$, procaine hydrochloride $2.5 \cdot 10^{-5}$, chlorpromazine $1.25 \cdot 10^{-4}$. Altogether 70 experiments were performed.

EXPERIMENTAL RESULTS AND DISCUSSION

Administration of aceclidine and serotonin in the above concentrations was followed invariably by a marked contractile response of the uterine cornu. Blocking SH-groups with cadmium sulfate was followed by total inhibition of spontaneous contractions of the uterine cornu. Against this background the effect of serotonin was almost completely abolished; it occurred in only 3 of 20 experiments and was much weaker than initially.

The contractile response to aceclidine either was absent (14 experiments) or was ill-defined (6 experiments). Meanwhile the contractile response to barium chloride was virtually unchanged (Fig. 1). Tests

Experimental Division, P. M. Buiko Kiev Research Institute of Pediatrics, Obstetrics, and Gynecology. (Presented by Academician of the Academy of Medical Sciences of the USSR A. I. Cherkes.) Translated from Byulleten' Eksperimental'noi Biologii i Meditsiny, Vol. 77, No. 4, pp. 19-21, April, 1974. Original article submitted May 14, 1973.

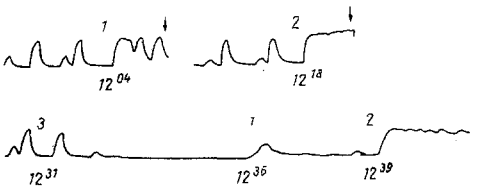

Fig. 1

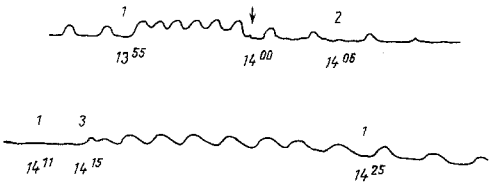

Fig. 2

Fig. 1. Role of SH groups in stimulant effect of aceclidine on the isolated rat uterine cornu: 1) aceclidine $4 \cdot 10^{-5}$; 2) barium chloride $4 \cdot 10^{-4}$; 3) cadmium sulfate $2 \cdot 10^{-5}$; arrow indicates rinsing with Kravkov's solution.

Fig. 2. Absence of stimulant effect of serotonin on the isolated rat uterine cornu after blocking of the SH groups with cadmium sulfate: 1) serotonin $4 \cdot 10^{-6}$; 2) cadmium sulfate $2 \cdot 10^{-5}$; 3) unithiol $2 \cdot 10^{-4}$; arrow indicates rinsing with Kravkov's solution.

of all substances were carried out at equal times (5-10 min) after the addition of cadmium sulfate. With intervals of 15-20 min between administration of the test substances (and subsequent rinsing) the contractile response of the uterus was the same as initially.

Unithiol completely or partly restored the spontaneous contractile function of the uterine cornu inhibited by cadmium sulfate. However, 3-5 min later the spontaneous uterine contractions again grew weaker. For a short time (3-5 min) unithiol increased the amplitude of the contractions of the intact uterine cornu also. After restoration of uterine contractions with the aid of unithiol the response to serotonin and to aceclidine was not restored (Fig. 2).

In agreement with the reported presence of D-serotoninergic receptors in the smooth muscle of the rat uterus [17, 18] it was shown that, after administration of the D-serotoninolytic drug chlorpromazine the contractile response of the uterine cornu to serotonin was completely blocked, whereas its response to serotonin after administration of the M-serotoninolytic drug morphine and the T-serotoninolytic procaine was the same as initially.

These experiments thus showed the role of the functional activity of SH groups of the myometrium in the mechanism of uterine contractions in response to serotonin and aceclidine. Since these substances interact selectively with D-serotoninergic and M-cholinergic receptors of the rat uterus, respectively, administration of cadmium sulfate can be presumed to block primarily those SH groups that are components of these receptor structures of the myometrium.

It might be supposed that cadmium sulfate, in the concentrations used, generally leads to inhibition of the contractile properties of the uterine smooth muscle. Against this view, however, the stimulant effect of the myotropic agent barium chloride on the uterus is preserved after administration of cadmium sulfate. Differences in the degree of sensitivity of the SH groups of receptor and extrareceptor structures of the myometrium to the blocking action of cadmium sulfate were confirmed by the experiments with unithiol. Unithiol restored the spontaneous contractile function of the uterus but its sensitivity to serotonin and aceclidine was not restored.

Trinus [16] observed that unithiol restores the sensitivity of the isolated rabbit uterine cornu to acetylcholine after blocking of the SH groups with cadmium chloride. This may perhaps be connected with species differences in the functioning of the cholinergic receptors of the uterus, as has been shown for the adrenergic receptors of that organ [6, 19, 20].

The results of the present experiments are evidence of functional differences between D-serotoninergic receptors in different situations, for mercuric chloride does not block the contractile response of the rat vas deferens to serotonin [4]. This result can be compared with differences in the response of the β_2-adrenergic receptors of the rat uterus and vas deferens to blocking of the SH groups with mercuric chloride [5].

The results suggest a role of the SH groups in the uterine receptor structures in the formation of the response of the myometrium to various sympathotropic and parasympathotropic agents.

LITERATURE CITED

1. N. B. Vysotskaya, E. I. Il'ina, and D. A. Kharkevich, Fiziol. Zh. SSSR, No. 9, 1076 (1960).
2. N. N. Demin, Biokhimiya, No. 3, 317 (1955).
3. I. V. Komissarov, Farmakol. i Toksikol., No. 2, 543 (1962).
4. I. V. Komissarov, Abstracts of Proceedings of a Plenum of the Committee of the All-Union Pharmacological Society [in Russian], Riga (1968), p. 25.
5. I. V. Komissarov, I. I. Abramets, and G. I. Reutskaya, in: Current Problems in Pharmacology, Proceedings of the 3rd Congress of Pharmacologists of the USSR [in Russian], Kiev (1971), p. 131.
6. G. S. Koroza, in: Current Problems in Pharmacology, Proceedings of the 3rd Congress of Pharmacologists of the USSR [in Russian], Kiev (1971), p. 132.
7. Kh. S. Koshtoyants and T. N. Turpaev, Dokl. Akad. Nauk SSSR, 53, No. 2, 181 (1946).
8. Ya. Z. Lemberskii and M. L. Tarakhovskii, Farmakol. i Toksikol., No. 6, 732 (1964).
9. S. A. Mirzoyan and S. V. Dovlatyan, Trudy Erevan. Med. Inst., No. 12, 27 (1962).
10. M. L. Tarakhovskii, Byull. Eksperim. Biol. i Med., No. 2, 83 (1959).
11. M. L. Tarakhovskii, Byull. Eksperim. Biol. i Med., No. 4, 72 (1970).
12. M. L. Tarakhovskii, in: Pharmacology and Toxicology [in Russian], No. 6, Kiev (1971), p. 95.
13. T. N. Turpaev, Biokhimiya, No. 4, 456 (1955).
14. T. N. Turpaev and T. T. Putintseva, Farmakol. i Toksikol., No. 2, 22 (1957).
15. F. P. Trinus, Farmakol. i Toksikol., No. 6, 532 (1959).
16. F. P. Trinus, Farmakol. i Toksikol., No. 3, 309 (1962).
17. J. H. Gaddum and K. A. Hameed, Brit. J. Pharmacol., 9, 240 (1954).
18. J. H. Gaddum and Z. P. Picarelli, Brit. J. Pharmacol., 12, 323 (1957).
19. S. Soszka, J. Urban, and R. Czekanowski, Proceedings of the 12th All-Union Congress of Obstetricians and Gynecologists [in Russian], Moscow (1971), p. 142.
20. M. Uszynski, J. Urban and R. Czekanowski, Ginek. Pol., 41, 961 (1970).