8. R. Gorman, S. Bunting, and O. V. Miller, Prostaglandins, 13, 373 (1977).
9. R. Griglewski, R. Korbut, and A. Ocetriewicz, Prostaglandins, 15, 637 (1978).
10. P. E. MacIntyre, L. R. Pearson, and L. J. Cordon, Nature, 271, 549 (1978).
11. P. E. MacIntyre, R. I. Nandin, R. D. Rosenberg, et al., Circulation, 62, 274 (1980).
12. S. Moncada, R. Griglewski, and S. Bunting, Nature, 263, 663 (1976).
13. M. Paulette and M. Jawahar, Circulation, 62, 192 (1980).
14. J. E. Tateson and J. R. Vane, Circulation, 13, 383 (1977).

MECHANISM OF THE MODULATING ACTION OF HISTAMINE ON EXCITATION AND CONTRACTION OF SMOOTH-MUSCLE CELLS OF THE URETER

N. G. Kochemasova, V. M. Taranenko, and M. F. Shuba

UDC 612.731:612.467].014.46:615.218.1

KEY WORDS: smooth muscles; ureter; histamine; phencarol; Na^+, Ca^{++}, and R^+ ions.

In previous investigations the writers showed that histamine increases the duration of the action potential (AP) plateau of smooth muscle cells (SMC) of the ureter, and it was postulated that lengthening of the AP plateau by histamine was due to increased potential-dependent sodium conductance of the membrane [6].

The object of the present investigation was to continue the study of this phenomenon.

EXPERIMENTAL METHOD

Experiments were carried out on segments of the whole ureter or segments of the circular layer of the ureter from guinea pigs by a double sucrose gap technique, with simultaneous recording of electrical activity and contractions [1]. The original Krebs' solution had the following composition (in mM): NaCl - 120.4, KCl - 5.9, $NaHCO_3$ - 15.5, $MgCl_2$ - 1.2, NaH_2PO_4 - 1.2, $CaCl_2$ - 2.5, glucose - 11.5. In sodium-free Krebs' solution all the NaCl was replaced by equivalent amounts of sucrose. Tetraethylammonium (TEA) was used in a concentration of 8 mM, histamine 10^{-6} g/ml, and phencarol* 10^{-6} g/ml.

EXPERIMENTAL RESULTS

APs and contractions of SMC of the ureter in Krebs' solution during the action of a depolarizing current on the strip (whole preparation), and anelectrotonic responses to the action of a hyperpolarizing current are shown in Fig. 1: Ia and IIIa. Addition of histamine (10^{-6} g/ml) to the Krebs' solution caused a very small decrease in membrane resistance, slight depolarization of SMC, and the appearance of anode-opening APs. The most characteristic features of the action of histamine in Krebs' solution were lengthening of the AP plateau and an increase in the amplitude and duration of contractions Fig. 1: Ib, c; IIIb, c. The increase in the duration of the AP plateau under the influence of histamine was not due to depolarization of SMC, for a shift of resting potential to the same level by the polarizing current caused only a negligible lengthening of the AP plateau. In addition, during repeated application of histamine depolarization of SMC was not always present, but the effect on the AP plateau remained.

To study the role of Ca^{++} ions in the histamine effect, in the next series of experiments the action of histamine on SMC of the ureter was studied in sodium-free Krebs' solution. The writers showed previously that AP of SMC of the ureter in sodium-free Krebs' solution on the addition of TEA, to inhibit potential-dependent outward potassium currents, consists of a spike component and a plateau, the amplitude of which is a direct logarithmic

*Quinuclidyl-3-diphenylcarbinol.

A. A. Bogomolets Institute of Physiology, Academy of Sciences of the Ukrainian SSR, Kiev. (Presented by Academician of the Academy of Medical Sciences of the USSR A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 94, No. 9, pp. 80-82, September, 1982. Original article submitted April 7, 1982.

 0007-4888/82/9409-1256$07.50

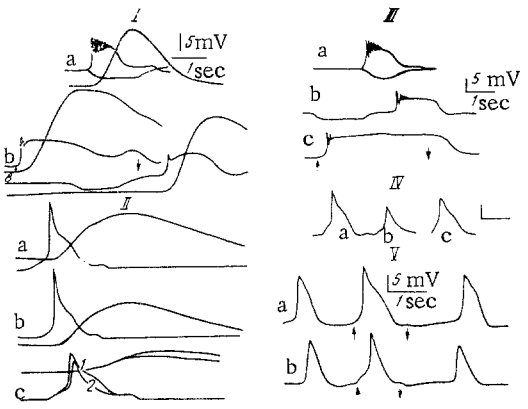

Fig. 1. Action of histamine (10^{-6} g/ml) on electrical and contractile activity of SMC in normal (I, II) and in sodium-free Krebs' solution with TEA (II, IV, V). Ia, IIIa) Action of depolarizing and hyperpolarizing current on electrical (top trace) and contractile (bottom trace) activity of SMC in normal Krebs' solution; Ib, c, IIIb, c) the same during action of histamine; II: a, c (1) — evoked APs and contraction in sodium-free Krebs' solution with TEA, b, c (2) — the same during action of histamine; IVa) evoked APs in sodium-free Krebs' solution with TEA, b) the same during action of histamine, c) the same after rinsing with Krebs' solution; V: a) spontaneous and evoked APs in sodium-free Krebs' solution with TEA; b) the same, during action of histamine. Arrows: depolarizing current on and off.

function of the external Ca^{++} ion concentration [4]. APs of SMC of the ureter, spontaneous and evoked by the depolarizing current, in sodium-free Krebs' solution and in the presence of TEA (8 mM) are illustrated in Fig. 1: II, IV, V. Addition of histamine to the sodium-free solution evoked an effect in SMC of the ureter opposite to that observed in the same muscle cells in normal Krebs' solution. In the absence of Na^{+} ions, when the AP plateau was due to increased membrane permeability to Ca^{++} ions, histamine caused a decrease in the amplitude and duration of the AP plateau (Fig. 1: IIb, Vb), accompanied by depression of the contractile response of the muscle cells (Fig. 1, IIb).

In some cases, especially on repeated application of histamine, besides a decrease in the amplitude and duration of the AP plateau, a decrease in amplitude of the spike component of AP also was observed (Fig. 1: IIc, IVb).

Since it was shown that the increase in the duration of the AP plateau under the influence of histamine is due to the response of SMC of the circular muscle layer and is absent in cells of the longitudinal muscle layer [2], the next step was to determine whether this effect of histamine in sodium-free Krebs' solution is found in the whole ureter, in cells of the circular muscle layer.

APs of SMC of the circular muscle layer of the ureter in response to stimulation with square pulses of direct current 50 msec in duration are shown in Fig. 2. As the data show, in Krebs' solution histamine increased the duration of both spontaneous (Fig. 2: Ib, c) and evoked (Fig. 2, Id) APs. Against the background of blockade of histamine (H_1) receptors by phencarol (10^{-6} g/ml) the histamine effect was absent (Fig. 2, II). In sodium-free Krebs' solution, but in the presence of TEA, histamine evoked a distinct decrease in the amplitude and, in particular, the duration of the plateau of both evoked (Fig. 2, IIIb) and spontaneous (Fig. 2, IIIc) APs. The addition of phencarol to sodium-free Krebs' solution with TEA was accompanied by an increase in amplitude of the fast component of AP and, in particular, in the duration of the AP plateau (Fig. 3). In sodium-free Krebs' solution, just as in normal Krebs' solution, phencarol blocked the histamine effect (Fig. 2, IV).

The results of these investigations show that histamine differs in its effect on the AP plateau of the SMC of the ureter in normal and sodium-free Krebs' solutions. In the first case it increases but in the second case it depresses the AP plateau. The fast con-

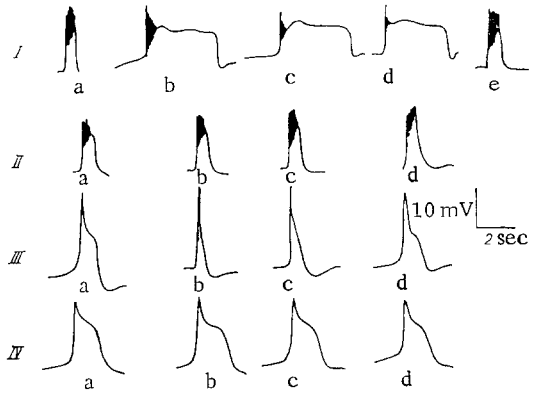

Fig. 2

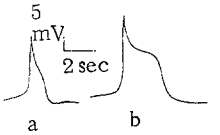

Fig. 3

Fig. 2. Action of phencarol (10^{-6} g/ml) on histamine effect in normal and sodium-free Krebs' solutions with TEA in smooth muscles of circular layer of ureter. 1) Evoked APs (stimulation by square pulse 50 msec in duration) in normal Krebs' solution before (a) and after (e) action of histamine. Spontaneous (b, c) and evoked (d) APs during action of histamine; II) evoked APs against the background of phencarol in normal Krebs' solution before (a), after (d), and during action (b, c) of histamine; III) spontaneous APs in sodium-free Krebs' solution with TEA before (a) and after (d) action of histamine. Evoked (b) and spontaneous (c) APs during action of histamine; IV) spontaneous APs against the background of phencarol in sodium-free Krebs' solution with TEA before (a), after (d), and during action (b, c) of histamine.

Fig. 3. Action of phencarol on AP in smooth muscles of circular layer of ureter. a) Spontaneous APs in sodium-free Krebs' solution with TEA, b) the same in the presence of phencarol (10^{-6} g/ml).

traction evoked by AP showed similar changes. In both cases the action of histamine on SMC was effected through activation of type H_1 histamine receptors, for phencarol blocked this action of histamine. Histamine receptors through which histamine exerts its action on the AP plateau are located on the membrane of SMC, mainly in the circular layer of muscles of the ureter. How can the opposite effect of histamine on the AP plateau in normal and sodium-free Krebs' solution be explained? In normal Krebs' solution the AP plateau is evidently sodium-calcium in nature, and the contribution of Na^+ ions to its formation is greater than that of Ca^{++} ions [3]. In sodium-free Krebs' solution the AP plateau is purely calcium in origin, and it is manifested only in the presence of TEA [4]. In the absence of TEA the high outward potassium current inhibits the inward calcium current, responsible for the AP plateau in sodium-free solution. In normal Krebs' solution, on the other hand, the inward sodium current is evidently sufficient for the AP plateau to arise even in the absence of TEA. In turn, the presence of the plateau facilitates development of the inward calcium current, which in the sodium-free Krebs' solution is inhibited by the TEA-sensitive outward potassium current. The hypothetical inward calcium current evidently takes part in activation not only of the contraction, but also of the so-called Ca-induced outward potassium current [5]. There is no doubt that under normal conditions this potassium current affects AP, depressing it, especially the plateau. Inhibition of the calcium current by histamine ought to lead to a decrease in the Ca-induced inward potassium current and, consequently, to lengthening of the AP plateau. It can thus be postulated that one cause of lengthening of the AP plateau of the SMC of the ureter under the influence of histamine is a decrease in the Ca-induced outward potassium current as a result of blocking by histamine of the potential-dependent calcium channels that were activated during plateau generation. To explain the role of the potential-dependent sodium channels in lengthening of the AP plateau under the influence of histamine, further investigations are needed.

The action of phencarol itself on AP of SMC of the ureter in sodium-free solution also deserves attention. This drug considerably increases AP, especially the plateau.

It can be tentatively suggested that either phencarol nonspecifically activates Ca-channels responsible for AP generation or it blocks H_1-receptors activated by tissue histamine released from mast cells, and so on. It is too early at present to decide whether the first or the second of these suggestions is to be preferred.

LITERATURE CITED

1. D. P. Artemenko and M. F. Shuba, Fiziol. Zh. (Ukr.), 10, No. 3, 403 (1964).
2. L. V. Baidan, S. M. Tishkin, and M. F. Shuba, in: The Physiology and Biochemistry of Mediator Processes [in Russian], Moscow (1980), pp. 18-19.
3. N. G. Kochemasova, Byull. Éksp. Biol. Med., No. 9, 9 (1971).
4. N. G. Kochemasova, Fiziol. Zh. (Ukr.), 28, 206 (1982).
5. R. W. Meech, Annu. Rev. Biophys. Bioeng., 7, 1 (1978).
6. M. F. Shuba, J. Physiol. (London), 264, 853 (1977).