EFFECT OF THE DEPHOSPHORYLATED CORE OF 2′,5′-OLIGOADENYLATE (2′,5′-ApApA) ON ELECTRICAL ACTIVITY OF THE SNAIL NEURON

I. N. Yakovenko and S. N. Omel'yanets

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Research workers are currently showing great interest in the system of adenyl oligonucleotides with a 2′,5′-phosphodiester bond [ppp(A2′p5′A)$_n$], which, together with cAMP, form the single regulatory system of cells [2]. The 2′,5′-oligoadenylates (2′,5′-A) are a chain of AMP residues, cross-linked by a 2′,5′-phosphodiester bond and a triphosphate group at the 5′-end of the molecule The 2′,5′-A inhibit growth, division, and differentiation of cells, accelerate the turnover and degradation of RNA, inhibit synthesis of DNA and protein, cause the appearance of antiviral resistance, of cells, and activate CAMP phosphodiesterase [2, 4]. The 2′,5′-A exhibit physiological activity mainly by reversible activation of the latent ribonuclease (Rnase İ) of cells. Besides 2′,5′-A, the 5′-dephosphorylated cores, in cells which can be phosphorylated by kinases present in the cell to 2′,5′-A, and can also competitively inhibit hydrolysis of triphosphorylated 2′,5′-A, also possess similar physiological activity.

The interest of research workers in 2′,5′-oligoadenylates is largely due to the search for new and effective antitumor and antiviral therapeutic agents [1]. The most promising of them are various analogs of the 5′-dephosphorylated core of 2′,5′-A due to their high efficiency of penetration through biological membranes and their marked physiological activity [1, 3].

There are no data in the literature on the presence of a 2′,5′-A system in nerve tissue structures, although it has been found in cells of the liver, kidneys, heart, testes, oviducts, and blood of animals and man [2]. It may accordingly be postulated that the 2′,5′-A system is a universal regulator of the biological activity of cells, and is also represented in nerve tissue. Accordingly we decided to study the effect of the dephosphorylated core of 2′,5′-A, namely 2′,5′-ApApA (Sigma, USA) on electrical activity of the giant neuron of the CNS of *Helix pomatia*.

EXPERIMENTAL METHOD

One microelectrode, filled with KCl (2.5 M) was inserted into neuron RPa2 of the right parietal ganglion of *H. pomatia,* the position of which is indicated in Fig. 1. The resistance of the microelectrodes was 10-30 MΩ. Membrane potential was recorded by means of an automatic recording potentiometer with time constant of 150 msec. The nerve ganglion was perfused with a solution of the following composition (in mM): NaCl — 90, KCl — 4, $CaCl_2$ — 7, $MgCl_2$ — 4, glucose — 10, Tris-HCl (pH 7.4) — 20.

After insertion of the microelectrode and the achievement of a stable electrical pattern, measurements were made of the bioelectrical activity of the neuron for 2 h after various times had elapsed from the beginning of observation. In the series of experiments to study the effect of 2′,5′-ApApA on the snail CNS, the ganglion was perfused for the first 2 min with a solution of the above composition, but which also contained 2′,5′-ApApA in a concentration of $5 \cdot 10^{-5}$ M. All the experiments were conducted at room temperature (18-20°C) in March and April.

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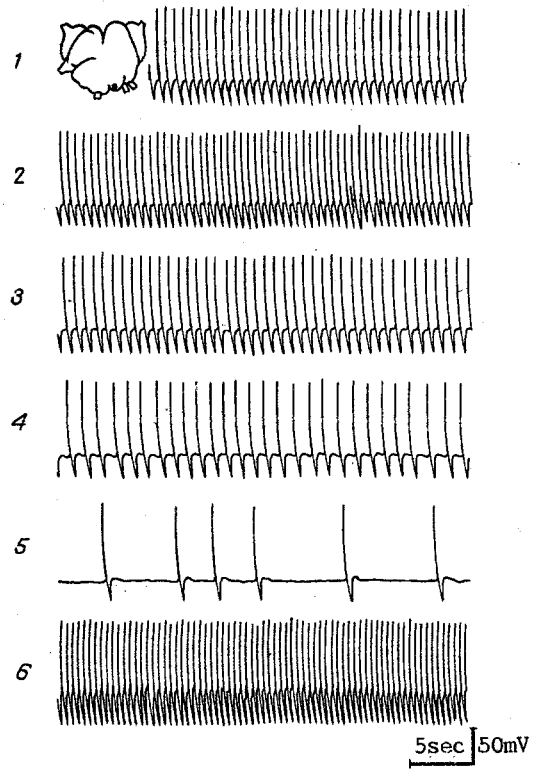

Fig. 1. Effect of the dephosphorylated core of 2′,5′-oligoadenylate (2′,5′-ApApA) on electrical activity of the *H. pomatia* neuron. 1) Initial electrical activity; 2) following exposure to 2′,5′-ApApA for 40-60 sec; 3) 130-150 sec; 4) 4 min; 5) 7 min; 6) 120 min.

EXPERIMENTAL RESULTS

On perfusion of the nerve ganglion of the snail with the control solution not containing 2′,5′-ApApA, the pattern of bioelectrical activity of neuron RPa1 was stable during observation for 2 h A very small increase in the frequency of action potential (AP) generation was observed 40-60 sec after the beginning of exposure to 2′,5′-ApApA. Later a gradual decrease was observed in the frequency of AP generation until 7 min after the beginning of exposure (Fig. 1), when only single nonregulatory bursts of AP were observed in the neuron. Changes in the frequency of AP 90 min after exposure to 2′,5′-ApApA remained similar, but after 2 h, the frequency of AP was higher than initially (Fig. 1). At the time of action of 2′,5′-ApApA and later the membrane potential, and also all characteristics of AP of the neuron were unchanged.

The investigation thus showed that the dephosphorylated core of 2′,5′-ApApA, during short-term exposure of the snail CNS in low concentration for a long time, can change electrical activity of neuron RPa2. In the present experiments the 2′,5′-ApApA was not applied directly to the soma of the test neuron, in which the nerve ganglion was located. An influence of 2′,5′-ApApA on the test neuron indirectly through other neurons and nerve tissue cells cannot therefore be ruled out. It can, however, be asserted that during exposure of the snail CNS to 2′,5′-ApApA, this compound causes prolonged and reversible inhibition of the frequency of AP of neuron RPa2, without affecting its membrane potential in this case. Consequently, the study of the 2′,5′-oligoadenylate system in nerve tissue, as possible regulators of the biological activity of electrically excitable cells, with the aim of creating fundamentally new neurotropic drugs, is accordingly promising.

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