Medical Hypotheses (2002) **58**(2), 171–176

doi: 10.1054/mehy.2001.1506, available online at http://www.idealibrary.com on IDEAL

A pulsed DC electric field affects P2-purinergic receptor functions by altering the ATP levels in *in vitro* and *in vivo* systems

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Summary Recently it was shown that extracellular ATP, acting through purinergic receptors, has many physiological functions, including opening of Ca^{2+}-ion channels, activation and mediation of signal tranduction mechanisms as well as activation of the pain sensation. Since electrical stimulation is also known to affect many signal transduction processes as well as the alleviation of pain, we hypothesized that electric stimulation may affect the extracellular release of ATP. We investigated the effects of a small DC electric field (10^{1}–10^{2} V m^{-1} range and with frequencies below 150 Hz) on the release of ATP *in vitro* (HeLa cells), and on the levels of ATP *in vivo* (the plasma of healthy volunteers). In HeLa cells ATP release was increased 50 fold, while the total amount of ATP in the cells was increased by 163%. In the plasma a significant decrease ($P < 0.05$) in ATP concentration was seen after electrical stimulation, in all the volunteers. The small DC electric field also affected the cAMP signal transduction system *in vitro* (HeLa cells and human lymphocytes) and *in vivo* (human plasma). Decreased levels of cAMP ($P < 0.05$) were seen in HeLa cells and increased levels of cAMP ($P < 0.05$) in isolated human lymphocytes. The cAMP levels in the plasma of the electrically treated volunteers were lower than control values. These results show that the frequency, waveform and signal strength of the applied electric field are suitable for effecting measurable changes on signal transduction *in vitro* and *in vivo*. © 2002 Harcourt Publishers Ltd

INTRODUCTION

Extensive research has shown that, apart from its well known intracellular effects, ATP also has many extracellular physiological functions (1). Extracellular ATP has been identified as a ligand, as a transmitter and also as a co-transmitter that affects numerous cellular functions by activating P2-purinergic receptors (see 1 for review). There are different types of P2-receptors, the two major classes being P2X- and P2Y-receptors. These receptors include several subtypes that can all be activated by extracellular ATP (1,2). The P2X receptors are ligand-gated ion channels whereas P2Y receptors are G-protein coupled (1–3). The ATP-dependent P2X ligand-gated channels can be permeable to either sodium, potassium or calcium ions. Via these channels, extracellular ATP can cause depolarization or an increase in the intracellular levels of calcium in activated cells (1,3). Five human P2Y ($P2Y_{1,2,4,6,11}$) G-protein coupled receptors have been identified and they all activate phospholipase C. Through the formation of IP3 (inositol-3-phosphate), intracellular calcium levels are

Received 6 February 2001
Accepted 17 August 2001

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