



Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Acupuncture: A novel hypothesis for the involvement of purinergic signalling

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ARTICLE INFO

Article history:

Received 14 May 2009

Accepted 15 May 2009

Available online xxx

SUMMARY

The hypothesis is summarised schematically in Fig. 1.

It is proposed that mechanical deformation of the skin by needles and application of heat or electrical current leads to release of large amounts of ATP from keratinocytes, fibroblasts and other cells in skin; the ATP then occupies specific receptor subtypes expressed on sensory nerve endings in the skin and tongue; the sensory nerves send impulses through ganglia to the spinal cord, the brain stem, hypothalamus and higher centres; the brain stem and hypothalamus contain neurons that control autonomic functions, including cardiovascular, gastrointestinal, respiratory, urinogenital and musculo-skeletal activity. Impulses generated in sensory fibres in the skin connect with interneurons to modulate (either inhibition or facilitation) the activities of the motoneurons in the brain stem and hypothalamus to change autonomic functions; specifically activated sensory nerves, via interneurons, also inhibit the neural pathways to the pain centres in the cortex.

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Background to purinergic signalling

ATP has been well established as an intracellular energy source for many years. However, in 1972 the concept of purinergic signalling was introduced, proposing that ATP also acts as an extracellular signalling molecule [1]. This concept was rejected by many for the next 20 years, but when the receptors for ATP and its breakdown product adenosine were cloned and characterised in the early 1990s, the concept was accepted and purinergic signalling is now a rapidly expanding field (see [2]). Purinergic-related drugs are being developed to treat a variety of diseases. For example, clopidogrel, an antagonist to the G protein-coupled receptor subtype on platelets that mediates aggregation, is a widely used drug against stroke and thrombosis (it made US\$8.6 billion in 2007). Clinical trials for other purinergic agents are in progress for bladder incontinence, dry eye, cystic fibrosis, osteoporosis, pain and cancer (see Fig. 1).

Supporting evidence

ATP release

While large amounts of ATP are released from damaged or dying cells, it has become clear that ATP transport from many cells in response to mechanical deformation, hypoxia, heat and electrical currents is a physiological event, which occurs without damage to the cells. For example, changes in blood flow results in shear stress releasing ATP from endothelial cells leading to vasodilation

via nitric oxide [3], and ATP is released from urothelial cells in the bladder and ureter leading to stimulation of suburothelial sensory nerves and from epithelial cells of the airways [3]. There is evidence for release of ATP from keratinocytes in response to mechanical stimulation [4,5] as well as fibroblasts [6] and immune cells [7].

ATP receptors on sensory neurons

Implicit in purinergic signalling is the presence of specific receptors for purines. Two families of purine receptors were recognised in 1978, P1 receptors for adenosine and P2 receptors for ATP. Two families of P2 receptors were proposed in 1985 and the molecular structure and second messenger agents involved discovered in the 1990s. Seven P2X ligand-gated ion channel receptor subtypes and eight P2Y G protein-coupled receptor subtypes are currently established (see [2]). P2X₃ homomultimer and P2X_{2/3} heteromultimer receptors were cloned in 1995 and shown to be located almost exclusively on sensory nerve endings [8].

These receptors have been shown with immunohistochemistry to be located on nerve endings in the skin and are particularly abundant in the tongue also used for acupuncture [9] (Fig. 2). Electrical recording from an isolated tongue-nerve preparation showed increased activity in the lingual nerves supplying the tongue during mechanical stimulation of the tongue that was mimicked by ATP and attenuated with P2X₃ receptor antagonists [10]. Similarly, distension of the ureter led to release of substantial amounts of ATP and evoked a discharge in the suburothelial sensory nerves that was mimicked by ATP and reduced by 2',3'-O-(2,4,6-trinitrophenyl)-ATP, a potent P2X₃ and P2X_{2/3} receptor antagonist (see [2]).

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