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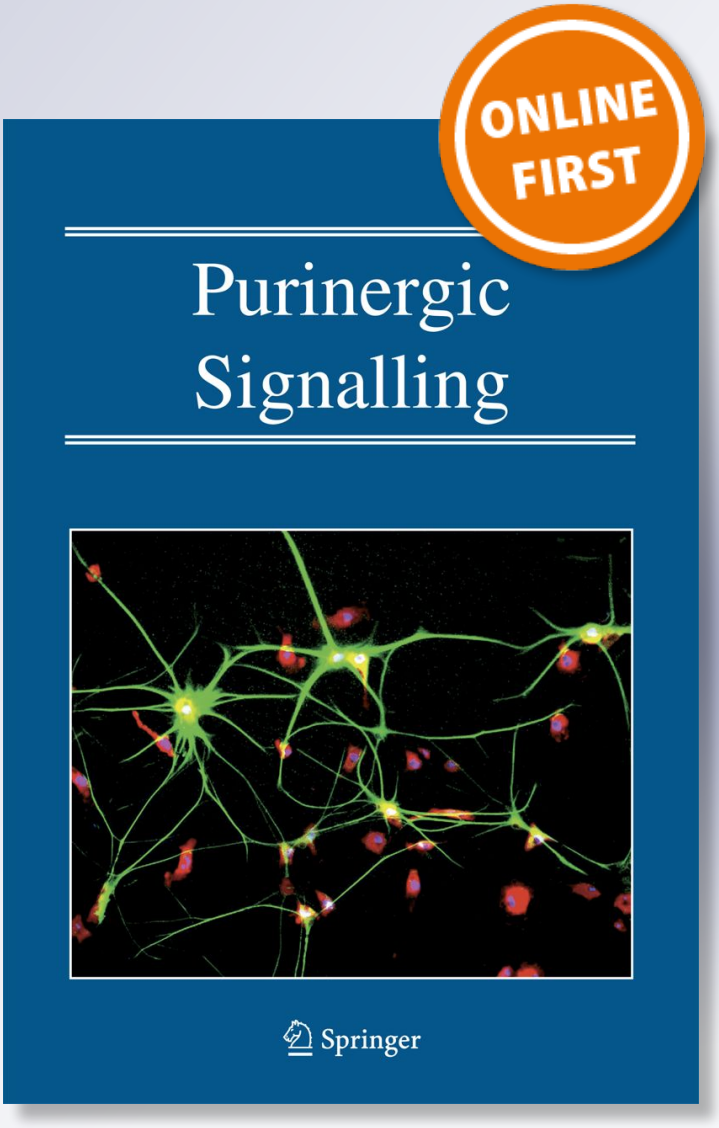

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BRIEF COMMUNICATION

The ATP or the natural history of neurotransmission

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ATP has become a personal obsession. I am arriving at this exciting field after working in exocytosis for decades. ATP is a natural component of chromaffin granules, the secretory organelle of adrenal chromaffin cells. These cells release catecholamines to the bloodstream as a response to stress stimuli [1]. Natural adrenal catecholamines comprise adrenaline and noradrenaline stored at amazingly high concentrations (0.5–1 M). These huge amounts together with the other soluble components (chromogranins, calcium, ascorbate, protons and ATP) should theoretically promote osmotic forces of about 1,500 mOsm! [2, 7]. To avoid the osmotic lysis of secretory vesicles, the solutes must be aggregated to reduce the tonicity; the main candidates to promote the aggregation have been chromogranins, the most abundant soluble proteins present in chromaffin granules and large dense core vesicles.

In an effort to demonstrate this vesicular role of chromogranins, we have studied the exocytotic responses in chromaffin cells from mice lacking in these proteins. Although the absence of chromogranins halves the vesicular amine content and impairs the ability of these secretory vesicles to uptake newly formed catecholamines, the concentration of catecholamines is still very high [5]. This fact made me recall an old paper performed by Ed Westhead's group (University of Massachusetts) in the mid-1980s. Using just an osmometer, they analyzed the osmotic properties of ATP/catecholamine mixtures reporting that this combination behaves as a non-ideal solute resulting in a reduction in the osmolaritay [6]. Recently, Dr. Westhead visited my laboratory for reanalyzing those results on the light of recent data. ATP is co-stored in chromaffin granules with catecholamines at proportion that ranges 1:2.5–6. With these numbers in mind, we obtained the data shown in Fig. 1. After reading the story of co-transmission [3], I guessed that ATP is not co-released with catecholamines; it is just the other way round: amines, peptides, amino acids and practically all of the secreted substances are co-released with ATP, who arrived first (Table 1).

As far as I know, all living eukaryotes have vesicles that accumulate ATP. This includes cells as primitive as *Giardia lambia*, *Trychomonas vaginalis*, *Toxoplasma gondii* or *Leishmania donovani*, microbes involved in several human parasite diseases [4]. In particular, *Giardia* is a very intriguing microorganism in that it lacks mitochondria and Golgi apparatus but still has dense granules that contain ATP. One can think that these acidic structures were created as a functional ATP

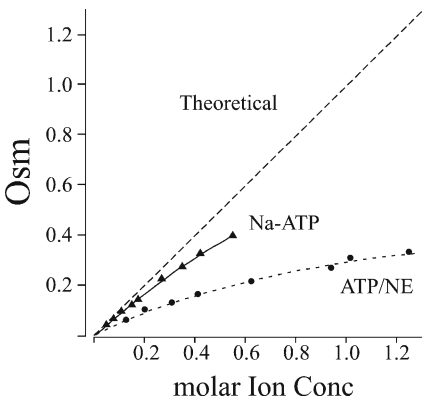

Fig. 1 ATP behaves as a non-ideal solute for creating osmotic forces. *Plots* show the osmolarit0y exhibited by Na–ATP and a mixture of ATP: norepinephrine at a proportion 1/2.8. These experiments were conducted by Dr. Edward Westhead using a vapour-phase osmometer during the short visit that he just run to my laboratory

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Table 1 Presence of ATP in secretory vesicles

Cell type	References
Adrenal chromaffin cells	Hillarp et al. (1955) *Nature* **176,** 1032–1033; Blaschko et al. (1956) *J Physiol* **133,** 548–557.; Carmichael et al. (1980) *J Neurochem* **35,** 270–272; Westhead & Winkler (1982) *Neuroscience* **7,** 1611–1614.
Astrocytes	Cotrina et al. (1998) *J Neurosci* **18,** 8794–8804; Guthrie et al. (1999) *J Neurosci* **19,** 520–528.
Cholinergic nerve skeletal junction	Forrester (1972) *J Physiol* **221,** 25P-26P; Luqmani (1981) *Neuroscience* **6,** 1011–1021.
Cholinergic terminal SNC	Burnstock (1977) *Fed Proc* **36,** 2434–2438; Richardson & Brown (1987) *J Neurochem* **48,** 622–630.
Chondrocytes	Graff et al. (2000) *Arthritis Rheum* **43,** 1571–1579.
Endothelial cells	Yegutkin et al. (2000) *Br J Pharmacol* **129,** 921–926; Bodin & Burnstock (2001) *J Cardiovasc Pharmacol* **38,** 900–908.
Erythrocytes	Sprague et al. (1998) *Am J Physiol* **275,** H1726–1732.
Exocrine pancreas	Novak (2003) *News Physiol Sci* **18,** 12–17.
Fibroblast	Gerasimovskaya et al. (2002) *J Biol Chem* **277,** 44638–44650.
GABA neurons	Jo & Role (2002) *J Neurosci* **22,** 4794–4804.
Glutamate neurons	Robertson & Edwards (1998) *J Physiol* **508 (Pt 3),** 691–701.
HIT cells	Lange & Brandt (1993) *FEBS Lett* **325,** 205–209.
Lung epithelial	Akopova et al. (2012) *Purinergic Signal* **8,** 59–70.
Mast cells	Bergendorff & Uvnas (1973) *Acta Physiol Scand* **87,** 213–222.
Oocytes	Nakamura & Strittmatter (1996) *Proc Natl Acad Sci U S A* **93,** 10465–10470; Maroto & Hamill (2001) *J Biol Chem* **276,** 23867–23872.
Osteoblasts	Genetos et al. (2005) *J Bone Miner Res* **20,** 41–49; Romanello et al. (2005) *Biochem Biophys Res Commun* **331,** 1429–1438; Orriss et al. (2009) *J Cell Physiol* **220,** 155–162.
PC12	Wagner (1985) *J Neurochem* **45,** 1244–1253.
Platelets	Holmsen & Weiss (1979) *Annu Rev Med* **30,** 119–134; Luthje & Ogilvie (1983) *Biochem Biophys Res Commun* **115,** 253–260.
Sympathetic nerves	Burnstock (1988) *Trends Pharmacol Sci* **9,** 116–117.
Torpedo electric organ	Dowdall et al. (1974) *Biochem J* **140,** 1–12; Zimmermann & Denston (1976) *Brain Res* **111,** 365–376.
β-cells	Hazama et al. (1998) *Pflugers Arch* **437,** 31–35.

reservoir to preserve it from cytosolic degradation in a cell that may not be efficient enough to produce ATP at a high rate. The conjunction of ATP-containing vesicles and constitutive exocytosis was probably the origin of (neuro)secretion in the days when life started. Later simple biochemical modifications on choline, histidine, tryptophan or tyrosine led to cholinergic, histaminergic, serotonergic and sympathetic transmission.

ATP being probably the first neurotransmitter, it seems plausible that the history of secretion started from the fusion of an ATP-contained vesicle with the cell membrane. Newly created transmitters found purinergic vesicles already made. All vesicles accumulate H^+: the pH, the electric gradient or both are required for concentrating most transmitters inside. The proton gradient is produced by the V-ATPase, which is also activated by ATP, another fact to think about. Nevertheless, although this commentary will not change any biological fact, we should consider that perhaps exocytosis of ATP is the pillar for understanding cell-to-cell communication.

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