

Neurotransmitters or Biomediators? The Cholinergic System in Protozoa

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The identification of the acetylcholine (ACh) dates back to the early twentieth century. In fact, it was described by the student Reid Hunt [1] in 1906 in adrenal extract of animals and, therefore, catalogued as a neurotransmitter [2]. During the following 40 years since the discovery of its neurotransmitter, the entire cholinergic system (ChS) was identified and its role in neurotransmission demonstrated [3]. In its classical connotation, the ChS is composed by a coordinated set of molecules, formed by the signal molecule, ACh and its muscarinic (mAChR) and nicotinic (nAChR) receptors, its biosynthetic enzyme, choline-acetyltransferase (ChAT, E.C. 2.3.1.6), the specific ACh lytic enzyme, acetyl-cholinesterase (AChE, E.C. 3.1.1.7), and other less specific choline esterases: butyryl-cholinesterase (BChE, E.C. 3.1.1.8), propionyl-cholinesterase (PChE, E.C. 3.1.1.8), together called pseudocholinesterases [4]. However, just ten years after the discovery of ACh, its identification in the fungus *Cleviceps purpurea* [5] pointed out that the term neurotransmitter was too confining. In the first half of the last century, Youngstrom (1938) [6] reported the presence of the cholinesterase (ChE) enzyme activity in the embryos of three amphibian species long before the onset of the nervous system. Later, with the discovery of the presence of ACh in Plants [7] and in the bacteria *Pseudomonas fluorescens* [8], its non-nervous role was clear. The presence and function of ChS in Protozoa has been less investigated than in the animals, sometimes with conflicting results and often the bibliographies are not easily available. This is the case of the studies of Beyer and Wense (1936) [9], Mitropolitanskaya (1941) [10] and Bullock and Nachmansohn (1942) [11]. The first one described the presence of ACh and ChE in the ciliate protozoa *Paramecium* sp. [9], while Bullock and Nachmansohn [11] and Mitropolitanskaya [10] denied the presence of ChE in both *Paramecium* sp. and some sponges (Porifera), while significant amounts of this enzyme were found in the Hydrozoa (Cnidaria) [11]; the first organism with a differentiated nervous system. In view of their results, Bullock and Nachmansohn [11] proposed that the nervous system requires ChE for its functioning and that, therefore, the phylogenetic appearance of ChE should coincide with the one of the nervous system. The paradigm represented by ciliated protozoa was later outcome by the speculation that the protozoa fibrillar structure connecting bases of the cilia is actually a primitive conducting and coordinating organ analogous to the nervous system. Thus, the presence of ChE in *Paramecium* sp. [9] and *Tetrahymena gelii* [12] could be correlated with both its primitive conductile system and its motility. This hypothesis was supported by the results of Bulbring, Lourie and Pardoe (1949) [13], which show that the highly motile, flagellated protozoa *Trypanosoma rhodesiense*, but not the amoeboid blood form of protozoa *Plasmodium gallinaceum*, had ACh as well as choline acetylase. The presence of a ChS in ciliated and flagellated protozoa was “recently” confirmed. In *Paramecium primaurelia* the presence of AChE-like protein was evidenced as well as the absence of molecule correlated to BChE [14]. The presence of ACh and ChAT was also characterized during the different stage of *P. primaurelia* life cycle and the role of ACh as a negative modulator of its sexual reproduction (conjugation) suggested [15]. In addition, a molecule correlated to AChE was detected in the ciliate *Euplotes crassus* [16], while in the ciliate *Colpoda inflata*, no ChEs activity was observed [17]. As *Colpoda* sp. peculiarly does not show sexual reproduction respect to both *Paramecium* sp. and *Euplotes* sp., the presence of the cholinergic system in the ciliate protozoa seems to be more correlated to the cell-to-cell interaction than the only cell motility [15-17]. Concerning the flagellate protozoa, in the parasite *Trypanosoma cruzi* the presence of nAChR was deduced by both the effect of nicotine on the intracellular calcium concentration and the ability of a membrane protein to bind nicotinic ligands such as carbamylcholine and nicotine [18]. The theory of Bullock and Nachmansohn [11] has been outcome several decades ago, thanks to a copious experimental evidence about the presence of cholinergic molecules in bacteria, fungi and algae [2]. To support of the inaccuracy of Bullock and Nachmansohn’s speculations [11], the presence of molecules

related to the cholinergic system was also shown in the amoeboid protozoa. Rubino and co-workers (1989) [19] demonstrated that the gene D2 of the slime mould *Dictyostelium* sp. encoded a serine esterase, with a strong sequence identity with both *Torpedo* sp. AChE and *Drosophila* sp. esterase. In particular, this protein is required for a proper aggregation and the subsequent development [19]. In *Dictyostelium discoideum* the presence of ChEs was demonstrated [20], their activity characterized [21] and their possible role in the developmental cycle pointed out [20-21]. Lastly, the role of ACh and AChE in the contractile vacuole activity of the *Amoeba proteus* was shown [22]. The presence of molecules correlated to the ChS in different protozoa meets well with the Mc Mahon (1974) [23] theory, which postulates that neurotransmitters have appeared early in evolution and therefore they are not peculiar characteristic of Metazoa, but they have been inherited from their protozoa ancestors. Actually, it is more correct to say that Protozoa and Metazoa have inherited molecules involved in neurotransmission from the common eukaryotic unicellular ancestor. This is in accord with the Miller-Urey experiment [24]. In fact, the experiment showed that the putative conditions on the primitive Earth favored chemical reactions, which synthesized more complex organic compounds from simpler inorganic precursors. Basically, choline would be produced this way, and, because the acetylation process is one of the most common reactions in nature, the ACh formation would have followed shortly after. Therefore, the ACh could have been originated 4 billion years ago, in the prebiotic earth, and used by the first prokaryotic organisms (3 billion years ago) as a biomediator, which was involved in the cell-to-cell communication, probably as hormone or molecule defense [2]. Later, the eukaryotic unicellular ancestor inherited the molecule, which, already a billion years ago, was used by protozoa in more complex cellular communications in the processes of differentiation, reproduction and cell adhesion [2,14-17,19-21]. Therefore, 500 - 400 million years ago, when the nervous system evolved, neurons did not “invent” but inherited the ACh, honing its use in faster and specialized communications.

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