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Cholinergic system neurochemistry toward therapeutic perspectives

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ABSTRACT

The physiological, therapeutical and experimental importance that the cholinergic system has, considerably increased the number of researches and publications that describe the different aspects of this system including neuropharmacology, cell biology and enzymology.

Hence, in the following lines some selected concepts are mentioned as illustrative examples to put a spot light on the cholinergic system from both functional and therapeutical viewpoints.

KEYWORDS

Cholinergic system;
Neurochemistry;
Therapeutic perspectives;
Nervous system;
Molecular mechanisms;
Neurological diseases.

OVERVIEW

Cholinergic system is among the most important systems for both physiology and pharmacology. Due to different factors; such as the availability of its ligands like atropine, a centrally-acting muscarinic cholinergic receptor antagonist[1], and cholinergic agonist oxotremorine[2]; this system has been studies not only in humans but also in some animals[3-6] and parasites[7] which allowed a good understanding of its functional and structural properties.

Cholinergic system is involved in a variety of functions including memory[8-11], digestion, cardiovascular functions, movement[12], motor control, behavioural learning[13], both acquiring and retrieving cocaine-associated memories[14], visuospatial attention[15], immune cells development[16] and cognitive functions[17,18]. Yet, new evidences are showing that future advances will describe further functions with probably more physiological implications.

MOLECULAR BASIS OF THE DISEASES, PATHOLOGICAL IMPLICATIONS AND THERAPEUTIC ILLUSTRATIONS

Cholinergic system has also been shown to play roles in some diseases and disorders such as Alzheimer's disease[4,17,19-21], Parkinson disease[22,23], depression[24], Multiple System Atrophy[25] and amyotrophic lateral sclerosis[26]. Moreover, during certain diseases, modifications and variations in cholinergic system have been reported. Indeed, basal forebrain cholinergic system atrophy has been associated with cortical amyloid burden[27], and post cerebral blood flow reduction-related central cholinergic dysfunction could be implicated in cognitive deficits resulting from chronic cerebral hypoperfusion[28]. On the other hand, new elements suggest more that amyloid-induced neuronal damage is

related to impairments in the synthesis of proteins related to the cholinergic system[29] especially since basal forebrain cholinergic system integrity is compromised by the disruption in nerve growth factor signaling via tropomyosin-related kinase A receptors[30]. These implications, that cholinergic system has in divers diseases, point the pathogenic importance of this system and thus, indicate the potential therapeutic benefits, of targeting such system in those diseases, which encourage further investigations to elucidate the pathogenesis underlying these disorders.

Targeting cholinergic system represents pharmacological approaches for many diseases and disorders. In fact, existent therapies are already based on such concepts which constitute the basic mechanisms of some medicines. For instance, while cholinergic receptors antagonists have been used as amnesic agent (muscarinic)[11], acetylcholinesterase inhibitors acting in the central nervous system may constitute pharmacological agents against traumatic brain injury mediated cognitive impairments[31] which would be an important advance in term of cerebral pharmacology.

In addition, involvement of cholinergic system within the sleep–wake cycle[32,33] may make this system a new therapeutic target for the future treatment of disorders such as insomnia and provide drugs that would constitute an alternative to those currently used.

More important, It has been recently reported that neurotrophins play an important role in the maintenance of cholinergic-neuron function[6] and that it is possible to rescue basal forebrain cholinergic neurons by administering neurotrophic factors and therefore, improving memory and learning performance[5]. This could constitute an important starting point mainly to treat neurodegenerative diseases.

PERSPECTIVES AND CHALLENGES

Fortunately, natural products are providing new agents that target or modify the cholinergic system[8,18,34] which will hopefully lead to new therapeutic approaches by either providing active compounds or molecules that would constitute starting point to develop chemically derived active compounds for both therapeutic usages and experimental investigations. Importantly, since some cholinergic receptors are G protein coupled receptors, which have been shown to be influenced by several factors[35,36], targeting the pathways related to the G protein coupled cholinergic receptors represents also therapeutic possibilities[37] that are worth exploring since it will, without any doubt, lead to identify new molecular targets among the intracellular enzymes and other biomolecules, implicated in the cytoplasm biochemical reactions, to develop new generations of molecular therapies.

Although therapeutic efficacy of targeting cholinergic system has been proven, it is strongly believed that this system still hides secrets and further investigations are required to elucidate the other functions that this system governs, or is involved in, and thus, consider the therapeutical applications it may have. Yet, pharmacovigilance and drug safety remain two important issues. Indeed, cholinergic system is in continuous interactions with the other systems mainly within the brain, these interactions is the result of the fact that the brain is a network within which drugs that influence a neurotransmitter-related system could influence the other neurotransmitters systems since they form, together, a strongly connected neural network[38]. Hopefully, new data and novel findings from different disciplines[10,12,39-42] will give more indications about the future orientations, that the investigations about cholinergic system, will have mainly in terms of therapeutic implications and physiological applications in divers research fields.

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Minireview

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