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Review

Anticholinergic activity in the nervous system: Consequences for visuomotor function

Preshanta Naicker [a,b], Shailendra Anoopkumar-Dukie [a,b], Gary D. Grant [a,b], Justin J. Kavanagh [a,c,*]

[a] Menzies Health Institute Queensland, Griffith University, Gold Coast, Queensland, Australia
[b] School of Pharmacy, Griffith University, Gold Coast, Queensland, Australia
[c] School of Allied Health Sciences, Griffith University, Gold Coast, Queensland, Australia

HIGHLIGHTS

- Little is known about the effects of anticholinergics on central motor processes.
- Cholinergic pathways play a role in oculomotor processes and pupil dynamics.
- This review outlines the effects that anticholinergics have on visuomotor function.

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ABSTRACT

Acetylcholine is present in the peripheral and central nervous system, where it is involved in a number of fundamental physiological and biochemical processes. In particular, interaction with muscarinic receptors can cause adverse effects such as dry mouth, drowsiness, mydriasis and cognitive dysfunction. Despite the knowledge that exists regarding these common side-effects, little is known about how anticholinergic medications influence central motor processes and fine motor control in healthy individuals. This paper reviews critical visuomotor processes that operate in healthy individuals, and how controlling these motor processes are influenced by medications that interfere with central cholinergic neurotransmission. An overview of receptor function and neurotransmitter interaction following the ingestion or administration of anticholinergics is provided, before exploring how visuomotor performance is affected by anticholinergic medications. In particular, this review will focus on the effects that anticholinergic medications have on fixation stability, saccadic eye movements, smooth pursuit eye movements, and general pupil dynamics.

Contents

* Corresponding author at: School of Allied Health Sciences, Griffith University, Gold Coast Campus, Queensland 4222, Australia.
E-mail address: j.kavanagh@griffith.edu.au (J.J. Kavanagh).

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1. Introduction

1.1. Acetylcholine

Acetylcholine (ACh) is a product of choline and active acetyl (CoA) and plays a critical signalling role in the nervous system [1,2]. ACh is present in the peripheral and central nervous system (CNS) where it is involved in a number of fundamental physiological and biochemical processes [1,3]. Peripherally, the parasympathetic nervous system is exclusively cholinergic as muscarinic (M) receptors are present on all effector cells [4,5]. ACh in the peripheral nervous system (PNS) is involved in pupillary and smooth muscle contraction, cardiovascular effects, and the stimulation of gastric and salivary glands [6–9]. Although ACh has a primarily excitatory role in the periphery, it acts more as a neuromodulator in the CNS [1,10]. ACh is transmitted diffusely within the CNS, where it is involved in processes such as arousal, attention and the control of movement [11,12]. M receptors mediate the functions of ACh and are abundantly distributed within the CNS in addition to non-neuronal tissues in the periphery [13,14].

1.2. Muscarinic (M) receptors and anticholinergic medications

M receptors belong to the family of receptors known as the G protein-coupled receptors (GPCR) [11,15] and can be classified into five distinct receptor subtypes: M_1 to M_5 [15–17]. Over the years, numerous studies have investigated the roles of each receptor subtype in mediating the actions of ACh [18], however it has proven challenging to elucidate the precise location and functional role of the various M receptor subtypes [17,19,20]. This is partly due to the lack of M receptor antagonists and agonists that demonstrate high selectivity for specific receptor subtypes, in addition to the fact that most tissues and organs in the body express more than one M receptor subtype [15,18,19]. However, gene targeting techniques that have generated mutant mouse strains deficient in each of the M receptor subtypes (knock-out mice) have been instrumental in providing an insight into the physiological roles of the various receptor subtypes [15,18,20–22].

In the periphery the M_1 receptor can be found in the sympathetic ganglia and salivary glands [19]. It is widely distributed in forebrain regions, including the striatum, cerebral cortex and hippocampus, where it comprises approximately 40–50% of the total M receptor population [19,22,23]. M_1 receptors are believed to be involved in many CNS functions [23]. Mice that lack the M_1 receptor exhibit cognitive impairments, where genetic studies have demonstrated that M_1 receptors play a role in higher cognitive functions such as learning and memory [17,19,23]. M_2 receptors are distributed in the periphery and throughout the brain [17]. In the periphery M_2 receptors are considered to play a functional role in regulation of the heart and in contraction of smooth muscle [17,19]. In addition, M_2 receptors might also be involved in the regulation of cognitive functions as M_2 knock-out mice also display cognitive impairments [17]. M_3 deficit knockout mice have demonstrated that M_3 receptors play a role in the contraction of smooth muscle, glandular secretion and pupil dilation [18,19,22]. Similar to the M_2 receptor it is widely distributed in the brain; however the functional role of M_3 receptors in the CNS is yet to be clarified [18,19]. In the periphery M_3 receptors can be found in the ileum and salivary glands. The distribution of M_4 receptors in the CNS is considered to be similar to that of M_1 receptors, where particularly high levels can be found in the striatum [19,22,23]. Studies with M_4 knock-out mice demonstrate that these receptors are involved in the regulation of dopaminergic activity and play a significant role in motor control [19,22]. M_5 receptors are minimally expressed in the nervous system and are believed to represent only 2% of the total M receptor population [18,22]. They can be found in peripheral and cerebral blood vessels where knock-out mice studies have shown that they are mostly involved in the reward system and regulation of blood flow in the brain [18,22]. Furthermore M_5 receptors are believed to be present in the striatum where they are considered to also potentially play a role in the regulation of dopaminergic neurotransmission [18,19,23].

Medications with anticholinergic properties can competitively block the actions of ACh on M receptors [14,24]. Anticholinergic medications can be classified as a tertiary or quaternary anticholinergics [14]. Anticholinergics with a tertiary ammonium structure can cross biological membranes such as the blood-brain barrier and thus are more likely to cause CNS adverse effects [14,25,26]. To the contrary, anticholinergics that are quaternary ammonium compounds cannot penetrate the BBB and as such, peripheral adverse effects are more likely to occur with this group of anticholinergics [14,27]. Medications with central and peripheral anticholinergic properties are readily available over-the-counter (OTC) in many countries where they are used in the treatment of nausea and vomiting, motion sickness or gastrointestinal cramps [25,28–30]. Adverse effects commonly associated with anticholinergic medications include dry mouth, mydriasis (pupil dilation), drowsiness and cognitive dysfunction [14,31]. Nevertheless, there are limited studies which have determined the implications of anticholinergic medications on motor control in healthy individuals.

2. CNS neurotransmitter interactions significant for motor control

The main sources of cholinergic projections in the CNS include the basal forebrain and the pedunculopontine nucleus (PPN) [32–35]. Cholinergic neurons in the basal forebrain are responsible for arousal, whereas cholinergic neurons in the PPN are considered to play a role in motor control as a function of projections to the striatum - a critical input nuclei of the basal ganglia [33,34,36]. Even though cholinergic interneurons only comprise a small proportion of neurons in the striatum, a high density of cholinergic markers implies that cholinergic neurotransmission plays an important role in the function of the basal ganglia [32,37,38].

The cholinergic system interacts with several other neurotransmitters in the CNS. However, there is particular significance in the well-documented interaction between ACh and dopamine (DA) in the basal ganglia [34,39,40]. In particular, a balance between these neurotransmitters is imperative for motor control [33,39,41–43]. Pre-clinical, clinical and neuropharmacology studies indicate that a dynamic balance exists between cholinergic and dopaminergic systems, where a neurotransmitter imbalance between cholinergic and dopaminergic systems results in movement associated CNS disorders [34,39,41,44]. Accordingly, most treatments for these CNS diseases focus on restoring the balance between neurotransmitter systems [34].

The influence of central anticholinergics on the balance between cholinergic-dopaminergic systems, and therefore movement, is particularly apparent in the treatment of Parkinson's disease, psychosis and schizophrenia [32,45]. Parkinson's disease is primarily characterised by a progressive loss of dopaminergic neurons in the striatum, which results in an overactive cholinergic system [45,46]. As such anticholinergic medications are used in the treatment of Parkinson's disease to decrease the degree of neurotransmission caused by striatal ACh [32,45]. In patients with schizophrenia and psychosis, central anticholinergics are used in the treatment or prevention of extrapyramidal side effects (drug induced movement disorders) caused by antipsychotics [4,47,48]. Antipsychotics block DA receptors and as a result decrease dopaminergic activity in cortical areas, thus causing extrapyramidal symptoms [47]. Central anticholinergics are suggested to be beneficial for use with antipsychotics as they block excitatory cholinergic activity in the basal ganglia and as such are effective in the treatment of extrapyramidal side effects [4,47].

3. The visuomotor system

Given that movements of the eye are coordinated by extraocular muscles where cholinergic pathways are implicated in the control of oculomotor processes [49–51], visuomotor assessments can provide for a