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Mini Review

Muscarinic Acetylcholine Receptors as Future Drug Targets in the Treatment of Schizophrenia

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Abstract

Schizophrenia treatment may be transitioning from traditional dopamine (DA) blockade to novel strategies involving cholinergic modulation of DA activity via muscarinic receptors. Current antipsychotics, effective against positive symptoms by blocking post-synaptic D2 receptors, often fail to adequately address negative and cognitive symptoms and are burdened by significant side effects. Cholinergic neurons regulate DA release pre-synaptically, influencing striatal DA levels crucial to schizophrenia pathology. Clinical trials of muscarinic receptor targeting therapies show promise in improving all symptom domains observed in patients with schizophrenia. This paradigm shift towards muscarinic receptor-based therapies offers a promising avenue for more effective and better-tolerated treatments for schizophrenia, highlighting the need for further research to fully exploit these therapeutic opportunities.

Keywords: Muscarinic Receptor, Schizophrenia, Pharmacology, Acetylcholine, Dopamine, Antipsychotics

Abbreviations:

DA: Dopamine

PFC: Prefrontal Cortex

CNS: Central Nervous System

PNS: Peripheral Nervous System

ACh: Acetylcholine

mAChRs: Muscarinic Acetylcholine Receptors

nAChRs: Nicotinic Acetylcholine Receptors

PNS: Peripheral Nervous System

5-HT: Serotonin

GABA: γ-Aminobutyric Acid

SNc: Substantia Nigra Pars Compacta

VTA: Ventral Tegmental Area

LDTg: Laterodorsal Tegmental Nucleus

PANSS: Positive and Negative Syndrome Scale

Introduction

Since the 1950's, the treatment of schizophrenia has been focused on dopamine (DA) blockade. The dysregulation of dopamine in the limbic striatum, associative striatum and prefrontal cortex (PFC) results in positive, negative, and cognitive symptoms [1]. The ability of antipsychotics to block post-synaptic D2 receptors has been shown to be efficacious when targeting positive symptoms. There has generally been a lack of efficacy when treating negative and cognitive symptoms, implying there is a multi-modal etiology associated with numerous neurotransmitters affecting all symptom domains [2]. Further limitations exist with the general side effect profile of many antipsychotics that includes: cardiometabolic effects, worsening cognition, movement disorders and sexual and endocrine dysfunctions. Most of these effects can be attributed to D2 blockade in various areas of the brain [3]. However, through cholinergic regulation of DA activity, it may be possible to treat schizophrenia while avoiding the side effects associated with direct DA blockade. Additionally, inhibiting DA release "up-stream" may improve negative and cognitive symptoms.

Acetylcholine (ACh) acts on two types of receptors, muscarinic acetylcholine receptors (mAChRs) and nicotinic acetylcholine receptors (nAChRs) in the central nervous system (CNS) and the peripheral nervous systems (PNS). The nAChRs are ligand-gated ion channels and several different subtypes have been identified, including: ten α (α1–10), four β (β1–4), γ, δ, and ε subunits. The mAChRs are G-coupled proteins and consist of 5 subtypes, M1, M2, M3, M4 and M5. The locations and role of these receptors vary on subtype, all of which are expressed in the CNS and in the periphery [4]. They control numerous functions including regulation of neurotransmitters, smooth muscle contractions, gland secretions, cardiac functions and memory. M1, M 3 and M5 are located post-synaptically and are excitatory. The M5 is the only mAChR to have been identified on dopamine neurons [5]. Inversely, M2 and M4 are expressed pre-synaptically, and their function is inhibitory. They are located in the midbrain (PFC and ventral striatum) on cholinergic neurons some of which originate in the lateral dorsal tegmental nucleus (LDT). They also exist on non-DA neurons for glutamate and GABA. Both agonism and positive allosteric modulation can induce a decrease in acetylcholine and a "down-stream" decrease in DA activity [4,6].

The concept that DA can be regulated "up-stream" via cholinergic input is not new. Activation of mAChRs has been shown to decrease psychotic symptoms and improve cognition in Alzheimer's patients [7]. The barrier in utilizing this mechanism for the treatment of schizophrenia and other psychiatric conditions has been based on the problematic side effect profile due to increased cholinergic activity in the periphery, which is now being re-explored with novel mechanisms to combat these effects. Additionally, regulating DA through mAChRs activation may provide additional mechanisms to better treat the negative and cognitive symptoms of schizophrenia. This review will introduce a possible paradigm shift in antipsychotic therapy which moves away from targeting DA and serotonin (5-HT) receptors directly and toward a more multi-mechanistic approach.

Mechanisms

Cholinergic neurons are known to form a complex network within the CNS which modulate the actions of neurotransmitters through mAChRs and nAChRs. The mAChRs physiological effects differ by receptor location and action. The M1, M3 and M5 utilize Gq-mediated signaling pathways which stimulate phospholipase C leading to increased intracellular calcium (Ca2+) levels and facilitate an excitatory effect [8]. Alternatively, M2 and M4 act through Gi- mediated signaling pathways, which results in cAMP accumulation and inhibitory effects [8]. The M1 and M4 receptors are mostly concentrated in the cerebral cortex and hippocampus, with the M1 predominantly acting post-synaptically in the PFC, and M4 can functions as pre- or post-synaptic hetero- or auto receptors and are additionally expressed in the basal ganglia and limbic system [9]. The M5 receptor locations in the body have been more difficult to identify but based on the literature have been identified on DA neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA) [5]. The M2 and M3 receptors are more widely expressed in the periphery and are responsible for many of the cholinergic effects in the PNS.

The mAChRs with known ACh modulation of DA in the CNS is the M1 and M4. The M4 receptors are expressed as pre-synaptic auto receptors in the SNc and VTA, where agonism of the M4 receptor results in decreased ACh release and secondarily diminishes the activity of DA neurons in the VTA, ultimately, decreasing DA release in the striatum [5, 8, 10]. The antipsychotic effects of a decrease in DA in the striatum via this mechanism has been observed with xanomeline, an M1 and M4 agonist [7, 12]. Moreover, "down-stream" effects of M1 receptor activation offers an additional mechanism for cholinergic regulation of DA. The PFC contains GABA interneurons which express the M1 receptors, and the activation of these receptors induces an increase of GABAergic activity. This increase of GABAergic activity secondarily inhibits glutamatergic pyramidal neurons, which project to the VTA and decrease glutamate activity. Since glutamate is responsible for DA excitation in the VTA, the reduced glutamatergic signal results in a decrease in DA activity in the striatum [8, 10, 11].

Lesser understood mechanisms of Ach-DA interactions have been observed with agonism or modulation of the M5 receptors and the nAChRs [5, 13]. Conceptually the M5 receptor subunit activation regulates DA neuronal activity and release in pertinent areas when discussing psychiatric symptoms. Similarly, studies in mice showed nAChRs are expressed pre-synaptically on DA neurons and activation by ACh enhances DA release alone and in conjunction with DA neuron activity [13]. Further studies are needed on the above mechanisms to better illustrate the possible effects these receptors have on DA, but their direct actions show the potential for therapeutic options.

Pharmacology

Several clinical trials are currently on-going utilizing M1 and M4 receptors as "up-stream" targets for DA modulation regarding schizophrenia and additional psychiatric disorders, the

most prominent candidate being KarXT (xanomeline+trospium). Xanomeline is an M1 and M4 agonist, which had shown success previously in Alzheimer's disease promoting cognition and decreasing psychotic symptoms [7]. Due to its lack of selectivity for the CNS, the effects in the periphery created an intolerable side effect profile. With the addition of trospium, a peripherally acting muscarinic antagonist, the undesirable cholinergic side effects of xanomeline have been mitigated [14]. Currently, it is in phase 3 clinical trials with promising results, showing a clinically significant decrease in cholinergic adverse effects, as well as a statistically significant decrease in Positive and Negative Syndrome Scale (PANSS) scores [12, 14]. Additionally, emraclidine, an M4 positive allosteric modulator, is in clinical trials with initial positive results [15]. Moreover, several other muscarinic receptor activators are in varying stages of clinical trials, highlighting these classes' therapeutic potential to offer new treatment options for those suffering with schizophrenia and other psychiatric disorders.

Discussion

The treatment landscape for schizophrenia has been dominated by post-synaptic DA receptor blockade, primarily targeting positive symptoms, while often falling short in addressing negative and cognitive symptoms. This limitation underscores the need for an approach that considers the multi-faceted nature of the disorder, involving various neurotransmitters beyond DA. Recent advancements highlight the potential of pre-synaptic cholinergic activation to modulate DA activity in an "up-stream" approach, offering a pathway to improve treatment outcomes while minimizing adverse effects associated with direct DA antagonism "down-stream". The mAChRs, particularly the M1 and M4 receptors play pivotal roles in this mechanism by exerting indirect effects on DA neurons, thereby influencing DA activity in critical brain regions involved in schizophrenia pathophysiology.

Emerging clinical trials, notably with compounds like KarXT demonstrating efficacy, underscore the promise of mAChR-based therapies in schizophrenia. These trials have demonstrated significant improvements in PANSS scores, indicating effective symptom management across multiple symptom domains of the disorder [12, 14]. Similarly, ongoing research into other mAChR modulation mechanisms, such as M4 positive allosteric modulators like emraclidine, further supports our understanding and potential treatment options for schizophrenia.

In conclusion, a potential paradigm shift in the treatment of schizophrenia is evolving beyond traditional DA centered approaches and towards a more comprehensive understanding of neurotransmitter interactions and their role in the pathophysiology of schizophrenia. Through ACh and its modulation of DA via mAChRs, a novel pharmacological approach may offer a promising therapeutic strategy. Future research and clinical trials will be pivotal in expanding the full therapeutic potential of mAChR-based therapies, potentially paving the way for safer and more effective treatments that address the complex symptoms associated with schizophrenia.

Acknowledgment

None.

Conflict of Interest

Dr. Jose Rey serves as consultant for the following pharmaceutical companies: Alkermes, Axsome Therapeutics, Bristol Meyers Squibb, Neurocrine Biosciences, Otsuka pharmaceuticals.

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