

Muscarinic Acetylcholine Receptors

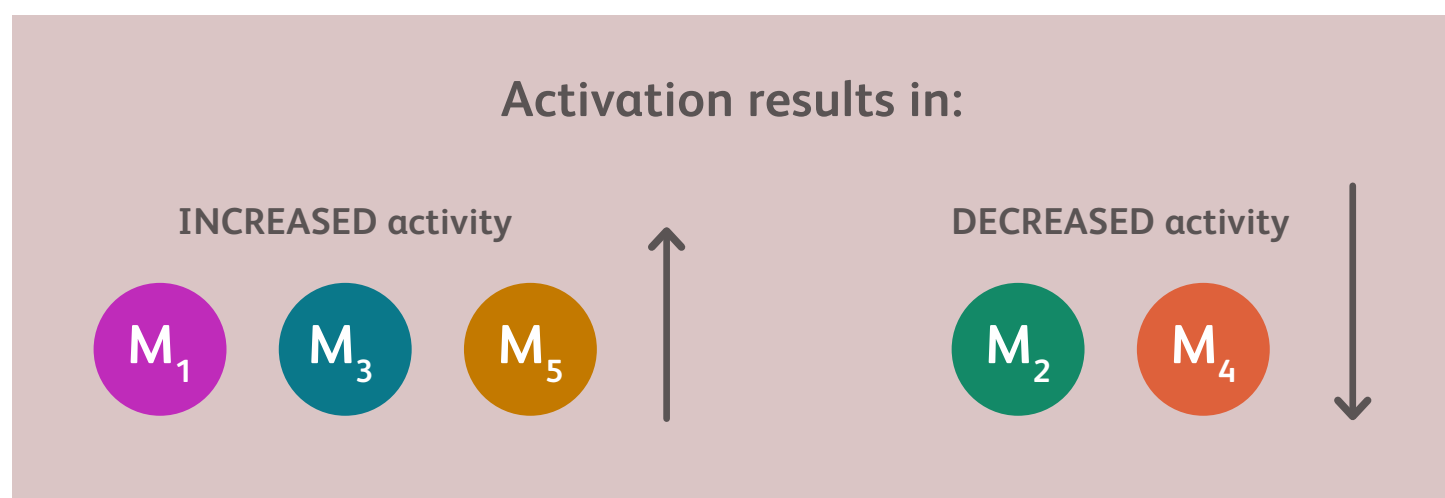
Muscarinic acetylcholine receptors (mAChRs) are a subfamily of G protein-coupled receptors that **regulate numerous fundamental functions** of the central and peripheral nervous systems. There are 5 subtypes¹:



Muscarinic receptors are distributed throughout many areas of the body and are responsible for various activities based on location and receptor subtype, including²⁻⁴:

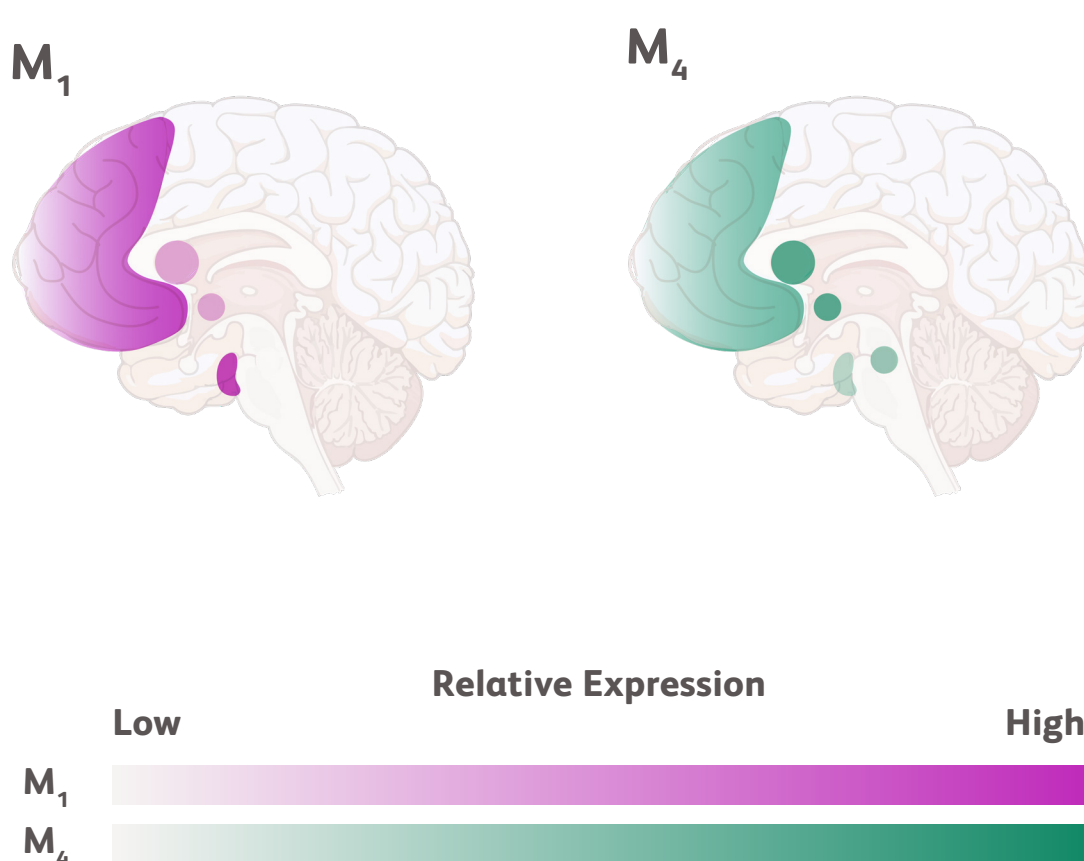
- Neuronal activation and signaling
- Behavior, learning and memory
- Cardiac function
- Smooth muscle function
- Function of glands involved in saliva and insulin production

The activation of muscarinic receptors results in either an **increase** or **decrease** in signaling within the cell depending on the receptor subtype³:



The role of M₁ & M₄ receptors in neurological disease

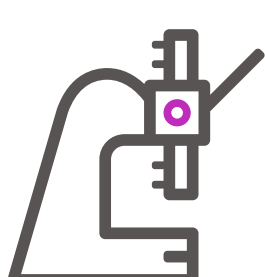
M₁ and M₄ receptors are present in **the central nervous system (CNS)** and are localized in brain regions responsible for a variety of functions, including behavior and cognition.^{3,5}



Certain **behavioral** and **cognitive** symptoms of neuropsychiatric diseases may be caused by impairments of brain circuits that impact and can be modulated by M₁ and M₄ receptor activity and/or expression as well as **acetylcholine**, the neurotransmitter and molecule that binds to mAChRs.

- Acetylcholine is released in the brain and binds to the **M₁ and M₄ receptors** to help regulate neurological function.
- M₁ and M₄ receptors are located in areas of the brain thought to be associated with behavioral and cognitive symptoms.
- Abnormal activity of M₁ and M₄ receptors in these areas of the brain may exacerbate those symptoms.⁶

Research implications



Research suggests that M₁ and M₄ receptors may play a key role in neuronal signaling in brain regions that are thought to be implicated in a variety of neuropsychiatric conditions, including^{6,7}:

- Schizophrenia
- Alzheimer's disease-associated cognitive impairment, psychosis and agitation
- Bipolar I disorder
- Irritability associated with autism

Bristol Myers Squibb is committed to rapidly advancing an innovative and diverse pipeline in neuroscience. We are researching key pathways to slow or stop disease progression and treat symptoms to achieve the greatest possible outcomes for patients.

REFERENCES

1. Kruse AC, Kobilka BK, Gautam D, Sexton PM, Christopoulos A, Wess J. Muscarinic acetylcholine receptors: novel opportunities for drug development. *Nat Rev Drug Discov*. 2014;13(7):549-560.
2. Abrams P, Andersson KE, Buccafusco JJ, et al. Muscarinic receptors: their distribution and function in body systems, and the implications for treating overactive bladder. *Br J Pharmacol*. 2006;148(5):565-578.
3. Kudlak M, Tadi P. Physiology, Muscarinic Receptor. PubMed. Last Updated August 8, 2023. Accessed October 29, 2024. <https://www.ncbi.nlm.nih.gov/books/NBK555909/>.
4. Paul SM, Yohn SE, Popielek M, Miller AC, Felder CC. Muscarinic Acetylcholine Receptor Agonists as Novel Treatments for Schizophrenia. *Am J Psychiatry*. 2022;179(9).
5. Fu L, Luo Y, Niu L, et al. M1/M4 receptors as potential therapeutic treatments for schizophrenia: A comprehensive study. *Bioorg Med Chem*. 2024;105:117728.
6. Dwomoh L, Tejada GS, Tobin AB. Targeting the M1 muscarinic acetylcholine receptor in Alzheimer's disease. *Neuronal signaling*. 2022;6(1): NS20210004.
7. Erskine D, Taylor JP, Bakker G, Brown AJH, Tasker T, Nathan PJ. Cholinergic muscarinic M1 and M4 receptors as therapeutic targets for cognitive, behavioural, and psychological symptoms in psychiatric and neurological disorders. *Drug Discov Today*. 2019;24(12):2307-2314.