A new aspect of cholinergic transmission in central nervous system

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In the central nervous system, acetylcholine (ACh) is an important neurotransmitter related to higher brain functions and some neurodegenerative diseases. It is released from cholinergic nerve terminals and acts on presynaptic and postsynaptic ACh receptors (AChRs). Following release, ACh is rapidly hydrolyzed and the resultant choline is recycled as a substrate for new ACh synthesis. However, this classical concept of cholinergic transmission is currently reevaluated due to new evidence. In the cholinergic synapse, ACh itself is taken up into postsynaptic neurons by a specific transport system (putative ACh transporter) and may act on AChRs at intracellular organelles (Golgi apparatus and mitochondria). Choline for ACh synthesis in cholinergic nerve terminals may be mainly supplied from choline at relevant concentration levels present in the extracellular space, rather than recycled from ACh-derived choline. Furthermore, ACh release is dominantly modulated by presynaptic M2/M3- but not M4-muscarinic AChRs. Recent evidence has reopened the issue of classical cholinergic transmission and cognition, and may provide a novel approach to rational drug development for the treatment of neurodegenerative disorders such as Alzheimer's disease.