

Scientific Article

Galantamine: Effect on nicotinic receptor binding, acetylcholinesterase inhibition, and learning

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Classical eyeblink conditioning is a well-characterized model paradigm that engages the septohippocampal cholinergic system. This form of associative learning is impaired in normal aging and severely disrupted in Alzheimer's disease (AD). Some nicotinic cholinergic receptor subtypes are lost in AD, making the use of nicotinic allosterically potentiating ligands a promising therapeutic strategy. The allosterically potentiating ligand galantamine (Gal) modulates nicotinic cholinergic receptors to increase acetylcholine release as well as acting as an acetylcholinesterase (AChE) inhibitor. Gal was tested in two preclinical experiments. In Experiment 1 with 16 young and 16 older rabbits, Gal (3.0 mg/kg) was administered for 15 days during conditioning, and the drug significantly improved learning, reduced AChE levels, and increased nicotinic receptor binding. In Experiment 2, 53 retired breeder rabbits were tested over a 15-wk period in four conditions. Groups of rabbits received 0.0 (vehicle), 1.0, or 3.0 mg/kg Gal for the entire 15-wk period or 3.0 mg/kg Gal for 15 days and vehicle for the remainder of the experiment. Fifteen daily conditioning sessions and subsequent retention and relearning assessments were spaced at 1-month intervals. The dose of 3.0 mg/kg Gal ameliorated learning deficits significantly during acquisition and retention in the group receiving 3.0 mg/kg Gal continuously. Nicotinic receptor binding was significantly increased in rabbits treated for 15 days with 3.0 mg/kg Gal, and all Gal-treated rabbits had lower levels of brain AChE. The efficacy of Gal in a learning paradigm severely impaired in AD is consistent with outcomes in clinical studies.

It has long been established that acetylcholine neurotransmission plays a crucial role in learning and memory, and more recently, the cholinergic system has been the focus of treatment for memory impairment in Alzheimer's disease (AD). The demonstrated role of acetylcholine in modulating the rate of learning in eyeblink classical conditioning in rabbits (1) makes this model system useful in preclinical investigations of cognition-enhancing drugs (2). More is known about the neural structures and systems that are involved in eyeblink classical conditioning than about any other learning and memory task. Although the neural circuitry essential for acquisition and retention of the conditioned eyeblink response resides in the cerebellum (3), the hippocampus is engaged during delay eyeblink classical conditioning (4). In the delay procedure, a neutral stimulus such as a tone conditioned stimulus (CS) is presented half a second before the onset of a corneal airpuff eyeblink-eliciting unconditioned stimulus (US). The organism learns to blink to the tone CS before the onset of the airpuff US, and the learned response is called the conditioned response (CR). It is our working hypothesis that selective loss of hippocampal pyramidal cells (5) and disruption of the septohippocampal cholinergic system in AD (6) impairs acquisition of delay eyeblink classical conditioning in AD beyond the impairment observed in normal aging. The hypothesis was supported (7, 8) and independently replicated (9).

Audioradiographic and histochemical studies of human brain tissue collected postmortem (10–13) and brain imaging studies in living AD patients (14) demonstrated specific loss of nicotinic cholinergic receptors and almost complete sparing of muscarinic cholinergic receptors in AD. Identification of nicotinic cholinergic receptors as the receptors impaired in AD led us to test a nicotinic cholinergic antagonist and nicotinic agonists in the animal model of eyeblink classical conditioning. By using a very low-dosage level of mecamylamine in young rabbits so that nicotinic cholinergic receptors would be selectively inhibited, we demonstrated a role for nicotinic cholinergic receptors in eyeblink conditioning because the acquisition of CRs was severely disrupted (15). A synthesized analog of the marine natural product anabaseine (16) called GTS-21 [3-(2,4-dimethoxybenzylidene)anabaseine] has been found to preferentially interact with $\alpha 7$ neuronal nicotinic receptors. Several doses of GTS-21 were administered to older rabbits, and this drug enabled older animals to produce significantly more CRs than did vehicle-treated older rabbits (17). Administration of nicotinic cholinergic agonists has promise in the treatment of cognition impairment in AD, but there are also some problems with this therapeutic strategy. It is difficult to establish the appropriate dose of a nicotinic cholinergic agonist, as higher-dose levels may cause desensitization rather than increased activation of nicotinic receptors (18). Additional problems include drug transport to the targeted nicotinic cholinergic receptors and the target selectivity of the receptor subtype. An alternative approach to drug treatment in AD is the application of allosteric modulators of nicotinic receptors (18, 19). Allosteric modulators are drugs that interact with the receptor through binding sites that are distinct from those for acetylcholine and nicotinic agonists and antagonists. Because these modulators are not directly involved in the neurotransmission process they affect, they typically do not induce compensatory processes that the agonists and antagonists induce. Thus, problems such as receptor desensitization and downregulation of expression can be avoided with allosteric modulators.

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