# Surprising discovery with Alzheimer's medication

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Alzheimer's disease (AD) is a debilitating brain disease that occurs in around 10% of the elderly and, as yet, there is no known cure. The most effective treatments are medications that attempt to increase the brain's levels of acetylcholine, an important neurotransmitter whose levels decrease with onset of disease. These drugs work by interfering with acetylcholine esterase (AChE), an enzyme that breaks down acetylcholine (Fig. 1).

Research by two scientists at the Weizmann Institute in Israel (http://www.weizmann.ac.il), has found that Rivastigmine (an AChE inhibitor) might be much more effective at raising acetylcholine levels than was previously thought [1]. Joel Sussman (Pickman Professor of Structural Biology) and Israel Silman (Bernstein-Mason Professor of Neurobiology) found that the drug has increased activity levels, lasting much longer than was suspected. X-ray crystals of the drug binding to AChE show a unique structure, which probably explains this lasting effect.

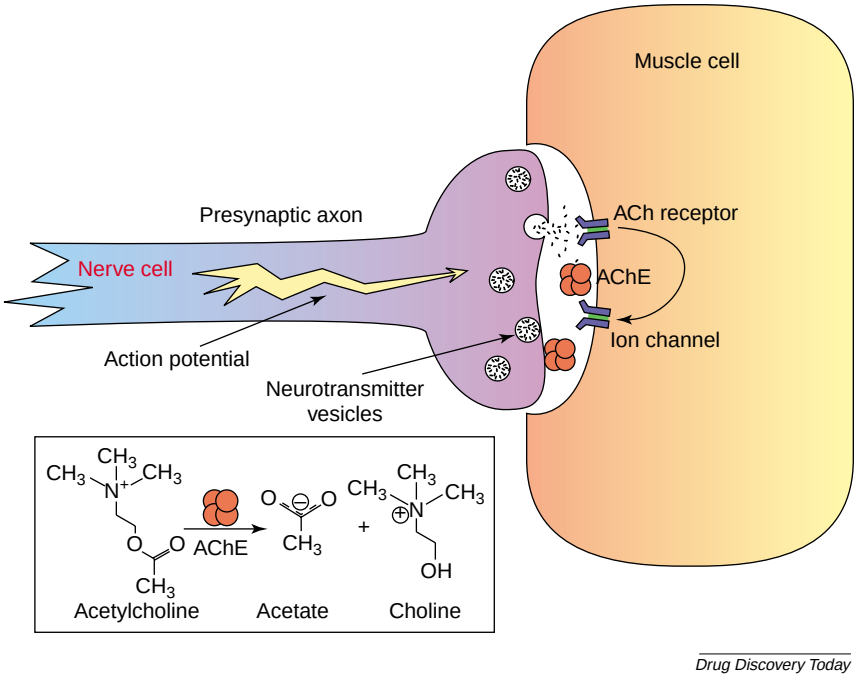


**Figure 1.** A schematic of a cholinergic synapse showing a nerve impulse traveling in the direction of the yellow arrow. In the presynaptic vesicle, the neurotransmitter acetylcholine (ACh) is represented by black flecks. As a nerve impulse travels down the neuron, ACh leaves the vesicle and crosses the synapse to bind with receptors on the next neuron. This perpetuates the nerve impulse. The ACh is then hydrolyzed by the enzyme acetylcholinesterase (AChE). Figure kindly provided by Joel Sussman (Weizmann Institute; http://www.weizmann.ac.il)

## Etiology and treatment of the disease

Alzheimer's disease is the most common cause of dementia in the elderly and its onset is difficult to diagnose. The physiopathology of the disease is complex and includes severe neuron and synapse loss, along with the accumulation of senile plaques, which contain the β-amyloid peptide. Evidence points to the accumulation of these plaques as crucial events in the development of the disease [2].

For decades, scientists have also known that neurotransmitter levels in the brain are altered with the disease. The most dramatic change is in the cholinergic system (see Fig. 1). As a nerve impulse travels down a neuron, acetylcholine is released at the axon, the nerve terminal. Acetylcholine then crosses over the synapse to bind with the next neuron, which then restarts the nerve impulse in the succeeding cell. To remove acetylcholine from the synapse, the enzyme AChE hydrolyzes the neurotransmitter.

With the onset of AD, the loss of neurons and axons leads to the release of less acetylcholine. With less neurotransmitter, it becomes more difficult to maintain nerve impulses and the transmission of information [3]. One way to get around this would be to give an acetylcholine substitute, however, none are currently available.

'Another way to increase acetylcholine is to inhibit the enzyme (AChE) that breaks acetylcholine down,' says Silman [4]. 'All the drugs currently available to increase acetylcholine work

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in this way.' Studies have shown that increasing acetylcholine by inhibiting AChE can ameliorate the cognitive deficits in the early stages of AD [4].

### Rivastigmine in action

There are around half a dozen AChE inhibitors on the market, including rivastigmine, which is sold under the name Exelon [5]. The drugs fall into three classes: tertiary amines, organophosphates and carbamates. Rivastigmine is a carbamate, and forms a covalent bond, which is slowly reversible, with AChE.

The Weizmann team performed kinetic studies of AChE with rivastigmine and found that the drug binds to AChE much more slowly and for a longer time period than expected, providing evidence of highly effective pharmokinetics.

X-ray crystallography determined why this is probably happening. Crystals of the fruitfly AChE, were soaked in rivastigmine. During binding, it was expected that rivastigmine would form a covalent bond and then split, with the leaving group washing into solution. The X-ray picture showed the leaving group was still bound to AChE. 'This is somewhat surprising,' says Sussman. 'It seems this causes the protein (AChE) to be distorted. So you've very slightly changed the 3D structure of the protein.'

'Most people would expect the leaving group to diffuse from the active site,' says Terrone Rosenberry, Professor of Medicine at the Mayo Clinic (http://www.mayo.edu). 'Instead, it is still sitting there at the active site, even though it is not linked to another part of the drug. So that's surprising.' Either the binding by the leaving group or the distortion of the AChE could explain why rivastigmine lowers the activity of AChE for such an extended period. 'It shows that rivastigmine might have better efficacy than these other drugs,' says Rosenberry.

### Kinetic studies

Sussman says the kinetic study shows that rivastigmine might bind to AChE for tens of hours. Shutting down the activity of AChE can effectively increase the levels of acetylcholine in the early stages of AD when the neurons are not making enough of the neurotransmitter. 'When the disease progresses to a point that little or no acetylcholine is being made, then this is not a good drug,' he adds.

Rosenberry says that besides the information on rivastigmine, this study also shows some interesting science about the nature of leaving groups that stay attached to their target. 'The science is interesting because it could apply to other substrates and substrate analogues of AChE for which there is no crystal data.'

### References


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# Superpeptide to treat *Candida albicans*

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A peptide analogue of α-melanocyte stimulating hormone (α-MSH) has been found to have potent antimicrobial activity against *Candida albicans*. This 'super' peptide killed nearly 100% of yeast cells in repeated experiments [1]. Its potency, coupled with the relative lack of toxicity of α-MSH peptides, suggest that this molecule holds the potential for use as a treatment for *Candida* and other infections in humans.

*Candida* species, including *C. albicans*, *C. parapsilosis*, *C. tropicalis*, *C. kefyr*, *C. krusei* and *C. glabrata*, are a component of normal human flora. 'We only have trouble with it when it gets out of bounds,' said James M. Lipton, founder and director of Zengen (http://www.zengen.com), who have developed the peptide against candidal vaginitis.

'The use of peptides is a hot area,' says Richard Meagher, Director of the Sramek Center for Cell Engineering at Rush-Presbyterian-St Luke's Medical Center (http://www.cancercelltherapy.org/). 'You can use them to fight infection, [and] you can use them to fight tumors,' he states.


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