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Therapy for Alzheimer's Disease

Symptomatic or Neuroprotective?

Ezio Giacobini

Department of Pharmacology, Southern Illinois University School of Medicine, PO Box 19230, Springfield, IL 62794-9230

Abstract

Therapeutic strategies aimed to treat Alzheimer's disease (AD) may either produce an attenuation of symptoms or slowdown deterioration by attenuating progression of the disease. Presently, cholinesterase inhibitors (ChEI) have shown the most promising therapeutic effects. The best documented clinical efficacy of ChEI are studies of THA (tacrine, tetrahydroaminoacridine). The results of five recent studies in a total of 1,242 patients are discussed. Based on differences from placebo in scoring, a gain of 2–12 (MMSE) or 5–6 (ADAS) in deterioration can be seen for a THA treatment of 2–3 mo duration. This suggests that if treatment with THA will be extended to a longer period, the drug effect may not be only a symptomatic improvement but also a slowdown of disease course. A similarity of THA's effect in AD with L-deprenyl effects in Parkinson's is suggested.

Index Entries: Alzheimer; cholinesterase; inhibitors; tacrine; deprenyl; Parkinson; neuroprotection.

Alzheimer's Disease and Parkinson's—Therapeutic Strategies

Therapeutic strategies aimed to treat Alzheimer's disease (AD) may either produce an attenuation of symptoms improving cognitive function and activity of daily living or slowdown deterioration by attenuating progression of the disease (Table 1). An example of the second mechanism could be the effect of L-deprenyl in Parkinson's *(1,2)*.

We may differentiate between "cellular" and "functional" neuroprotection (Table 1). Cellular neuroprotection may rescue nerve cells, slow down deterioration, and improve function above the level normally seen in patients at that particular stage of the disease (Table 1). Functional neuroprotection instead implies symptomatic improvement as well as slowing down of progression of the disease (Table 1). Finally, the effect of the drug may be only symptomatic. An example is L-DOPA treatment of Parkinson's.

Effect of Treatment on Decline of Cognitive Impairment in Alzheimer's Disease

Figure 1 shows a model of the course of decline of cognitive function in patients with probable or definite dementia of the Alzheimer type over a period of 7 yr from first to last evaluation. Overall severity of dementia is reported as a percent decline of cognitive impairment. The curve of decline is a modification of the model proposed by Haxby et al. *(3)*. Using the Wechsler Adult Intelligence Scale, the Dementia Rating Scale (DRS), and the Minimental State Examination (MMSE) at approximately annual intervals, Haxby et al. *(3)* demonstrated a

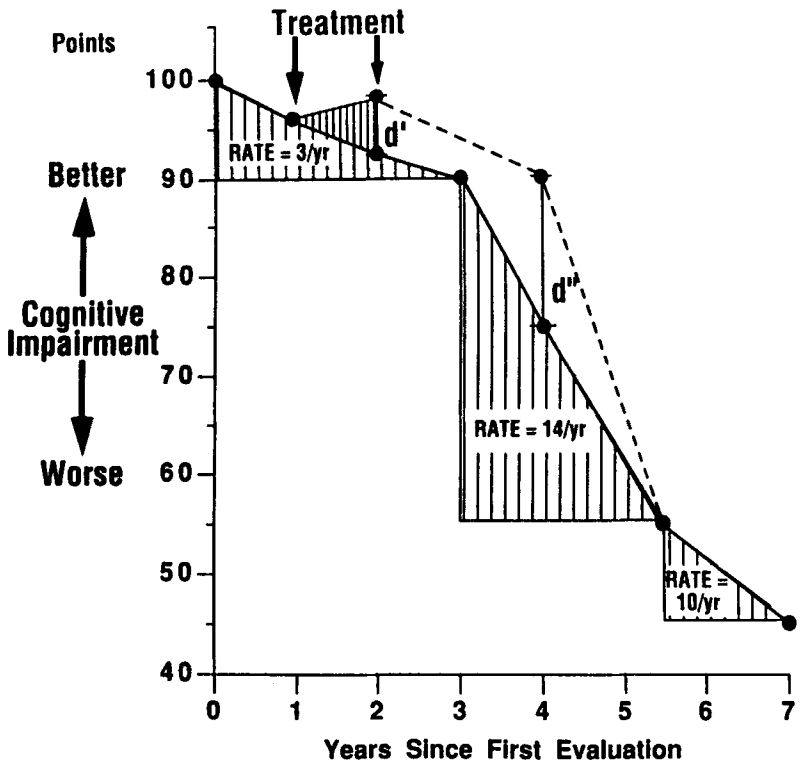

Fig. 1. Model of time course of cognitive decline in Alzheimer's disease patients from first to last evaluation. The theoretical rate of decline in the different phases is indicated (●---●). Rate of decline after treatment (●—●). d' and d'' indicate differences in decline of treated vs untreated patients.

Table 1
Differences: Symptomatic vs Neuroprotective

	Slows down deterioration	Improves function	Rescues cells
Cellular neuroprotection	+	±	+
Functional neuroprotection	+	+	–
Symptomatic effect	–	+	–

biphasic trajectory of decline in patients with AD. The curve of Fig. 1 shows an initial minimal rate of decline of 3 points/yr during a period of 3 yr.

We may superimpose to the theoretical curve of decline a curve of treatment starting 1 yr after the first evaluation and continuing for 12 mo. After a small but significant change during which the patients show symptomatic improvement, a new decline is seen at 12 mo. If treatment is able to slow down deterioration, the two curves (treatment vs nontreatment) should be parallel. This phase could last for several months after cessation of the treatment.

Clinical Effects of Cholinesterase Inhibitors

In treatment of AD, cholinesterase inhibitors (ChEI) have shown the most promising effect of any drug *(4)*. Cholinesterase inhibitors aim to preserve and enhance the physiological effect of acetylcholine (ACh) by increasing its level to close to normal concentrations in surviving cholinergic synapses.

The best documented clinical efficacy of ChEI relates to several studies of THA (tacrine, tetrahydroaminoacridine). Table 2 summarizes the results of five recent studies using similar methods of assessment of cognitive function in a total of 1,242 AD treated patients.

If these results with THA will be confirmed for other ChEI as well, they would suggest not only a symptomatic improvement but a real slowdown of the disease course with attenuation of the progression.

A Possible Mechanism of Neuroprotection

A possible mechanism to explain a slower deterioration of the AD patient resulting from CNS cho-

Table 2
Clinical Efficacy of Tacrine for Alzheimer's Disease

Authors	Type of study[a]	Nr. of pat.	Max dose mg; duration, wk	Points difference from placebo MMSE	Points difference from placebo ADAS	Deterioration gain, mo	Percent pat. improved
Gauthier et al. *(7)*	DB-CO-M	52	100 8	1		2	(75)
Eagger et al. *(8)*	DB-CO-PC	65	150 13	3–4		6–12	45
Davis et al. *(9)*	DB-PC-M	632	80 8		2.4	5	34
Farlow et al. *(10)*	DB-PC-M	468	80 12		4	6	51
Alhainen *(11)*	DB-PC	25	100 7	≥3		≥6	44

[a]DB = double-blind; CO = crossover; PC = placebo controlled; M = multicenter; MMSE = minimental state examination (0–30); ADAS = Alzheimer's disease assessment scale (0–70).

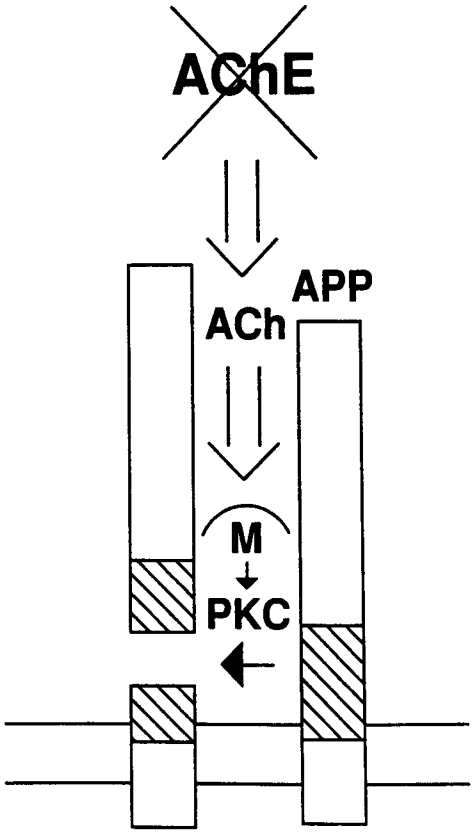

Fig. 2. Mechanism of action of AChEI on normal APP processing through muscarinic (M) receptor and protein kinase C (PKC) activation. *See text.*

linesterase inhibition can be found in recent experimental data indicating that cholinergic agonists may regulate processing and secretion of the β/A_4 amyloid precursor protein (APP) by increasing protein kinase C (PKC) activity of target cells *(5,6)*. Long-term acetylcholinesterase (AChE) inhibition by increasing the level of ACh to close to normal concentrations in the surviving synapses in the AD brain may activate the normal APP processing, which involves cleavage of full-length APP within the β/A_4 domain (Fig. 2). This effect could presumably slow down or preclude the formation of amyloidogenic APP fragments. Other possible mechanisms related to AChE inhibition may be neurotrophic effects of ACh receptor stimulation promoting regeneration or cell rescue and, therefore, slowing down deterioration. Both hypotheses of APP stimulation and trophic neuroprotection await demonstration at preclinical as well as clinical levels.

Acknowledgments

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