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Propentofylline
A Viewpoint by Peter Schubert

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The molecular and physiological events which cause dementia have yet to be fully clarified. This has precluded the development of a primary therapy aimed at the underlying disease process; such a therapy could be used in addition to symptomatic treatments aiming to overcome the impairment of cholinergic neuronal systems. However, there is accumulating evidence that glial cell activation is a common pathogenic factor in the generation of secondary nerve cell damage after stroke or brain trauma and in the development of vascular or primary degenerative dementia. The modulation of such glial cell reactions is a primary effect of propentofylline, which also protects against ischaemia-induced damage. Current *in vitro* studies indicate that propentofylline inhibits several potentially cytotoxic properties of activated microglial cells, helps to restore the properties of differentiated astrocytes and stimulates the formation of neurotrophic factors. These effects are largely associated with the activity of propentofylline as a highly selective phosphodiesterase inhibitor which modulates the delicate balance between the second messengers calcium (Ca^{++}), cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate. By reinforcing and/or mimicking the effects of adenosine on the Ca^{++}- and cAMP-dependent signalling cascade, propentofylline may act by strengthening the effects of an endogenous cell modulator which has evolved to regulate the complex molecular signalling underlying glial cell activation and related diseases. This may provide a therapy for dementia which has only a minor risk of undesirable side effects. ▲

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Propentofylline
A Viewpoint by Hans-Jürgen Möller

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Dementia is becoming an increasingly important medical and socioeconomic problem as the number of patients with the disease increases. The prevalence of dementia is high and is increasing in those aged 65 to 85 years. Most dementia in the elderly is caused by Alzheimer's disease, although vascular dementia or a combination of vascular and Alzheimer-type dementia are also common.

Several factors have contributed to a certain degree of nihilism regarding pharmacological treatment for dementia. The efficacy of most traditional nootropics has yet to be demonstrated and differences between proven nootropics and placebo have been relatively small. Furthermore, clinical methodology in this indication has been underdeveloped for some time.

Nevertheless, nootropic agents do have a place in the treatment of dementia. A most promising approach in recent years has been the development of cholinergic drugs based on the acetylcholine deficit hypothesis of Alzheimer's disease. In particular, several acetylcholinesterase inhibitors have proved clinically effective. The introduction of tacrine was a breakthrough in the field of antidementia therapy; however, the tolerability profile of this agent is not ideal, and its relative efficacy compared with that of placebo, like that of other cholinergic agents, is moderate. Thus, there is a need to continue the development of other classes of antidementia drugs.

Xanthines have been investigated for many years as potential treatments for dementia. Propentofylline is a recently developed xanthine derivative which has several potentially relevant pharmacological mechanisms and exhibits cognition-enhancing and neuroprotective properties. In placebo-controlled clinical studies, propentofylline induced significant clinical improvement of cognitive disturbances in patients with mild or moderate Alzheimer's disease or cerebrovascular dementia. It was able to prevent clinical deterioration over 12 months. Of greatest clinical interest, propentofylline appears to be generally well tolerated. Headache, dizziness and gastrointestinal disturbances are the most common adverse events.

Thus, propentofylline seems to be a valuable

therapy for patients with Alzheimer's disease or vascular dementia. ▲

531205

Propentofylline

A Viewpoint by Fiona E. Parkinson
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The prevalence of dementias is increasing in the aging populations of developed countries. Propentofylline is a novel xanthine derivative that is in late phase clinical development for the treatment of dementias related to Alzheimer's disease or cerebrovascular disorders.

Preclinical studies demonstrate that propentofylline significantly reduces neuronal damage following cerebral ischaemia in rodents. The neuroprotective effects of propentofylline appear to be due to potentiation of adenosine receptor activity, since propentofylline blocks cellular uptake and elevates extracellular levels of adenosine in ischaemic rodent brain. Adenosine is an endogenous neuromodulator that inhibits release of the excitatory neurotransmitter glutamate and has vasodilatory and antithrombotic properties, a combination of effects that is beneficial for neuronal survival following ischaemic episodes.

In addition to effects attributed to inhibition of adenosine uptake, propentofylline can inhibit free radical production by cultivated microglial cells, inhibit proliferation of astrocytes, and stimulate nerve growth factor production, effects that may reduce neuronal loss associated with neurodegenerative diseases.

Placebo-controlled studies in patients with dementia who were treated for up to 12 months indicate that propentofylline prevented clinical deterioration and produced significant clinical improvement in cognitive function. To date, human and animal studies are encouraging and indicate that propentofylline reduces neuronal loss due to acute or chronic disease processes. ▲