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Galantamine. A novel treatment for Alzheimer's disease

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The cause of Alzheimer's disease has not been fully elucidated, but over the past 20 years there have been major advances in understanding the neuropathological and neurotransmitter basis of the cognitive impairment, the hallmark of this devastating disease (Davies & Maloney 1976). Of major importance to the development of a rational pharmacotherapy was the discovery of selective deficits in the concentrations of the neurotransmitter acetylcholine (ACh), particularly in the basal nucleus of Maynert (Whitehouse et al 1982). Coupled with evidence from experimental animals, these discoveries resulted in the 'cholinergic hypothesis' of memory dysfunction, originally proposed in 1982 (Bartus et al). These concepts stimulated clinical trials in patients of various pharmacological interventions aimed specifically at the restoration of central cholinergic neurotransmission (Mohs et al 1981).

Whilst clinical studies, with ACh esterase inhibitors such as physostigmine and tacrine provided encouraging evidence of improvement in cognition, full clinical exploitation of these drugs has been hampered by pharmacodynamic, pharmacokinetic and tolerability limitations. Nevertheless, this research stimulated the search for second generation ACh esterase inhibitors with improved selectivity and tolerability profiles. One particularly promising drug, now in advanced clinical development, is galantamine hydrobromide.

Galantamine is a tertiary phenanthrene alkaloid originally extracted from the Caucasian snowdrop, *Galanthus worownii*, by Bulgarian researchers almost fifty years ago, shortly afterwards from *Lycorus radiata* and subsequently from various *Narcissus* and *Amaryllidaceae* species. Botanically derived galantamine is the optically active (−) enantiomer, the pharmacologically active form. The majority of the research and clinical studies completed to date has been performed with the bioextracted material, although the drug has been synthesized and large scale chemical production achieved.

Galantamine is a reversible, competitive, inhibitor of ACh esterase with high lipid solubility which readily enters the CNS (for review see Harvey 1995). The compound exhibits selectivity for ACh esterase vs butrylcholinesterase and in-vitro and in-vivo studies demonstrate the potentiation of various functional effects of ACh. There is some evidence that galantamine exhibits selectivity towards nicotinic as opposed to muscarinic ACh receptor-mediated phenomenon. Receptor binding and cellular electrophysiology studies with cultured hippocampal neurones (Maelicke provide a possible explanation whereby galantamine may selectively facilitate the nicotinic actions of ACh via an indirect, allosteric, mechanism.

Russian researchers first demonstrated in 1972 that galantamine reversed scopolamine-induced amnesia in mice. Beneficial effects upon memory have also been demonstrated in the rat using maze learning and passive avoidance paradigms. However, it was not until 1986 after the cholinergic hypothesis of memory impairment had been proposed, that the first clinical trials of galantamine in Altzheimer's disease were initiated. Results from these and subsequent trials have demonstrated unequivocal effects on cognition as shown by improvements in primary and secondary measures of clinical efficacy (Rainer 1997; Wilcock & Wilkinson 1997). The pharmacokinetics and metabolism of galantamine make it an ideal drug for clinical use. Activity in man is attributable to the parent compound which has a plasma half life consistent with convenient twice daily dosing (Kewitz 1997). The drug exhibits insignificant plasma protein binding and it has a low potential for drug interactions. Galantamine thus shows a very promising potential in the treatment of Altzheimer's disease.

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