Monitor

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Chemistry

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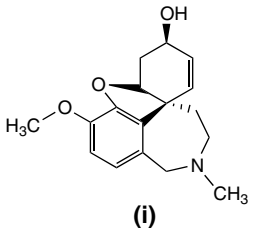
Molecules

Galantamine: new developments on its mechanism of action

Galantamine (**i**), which was recently approved by the FDA, is an acetylcholinesterase inhibitor that has a unique pharmacology among this class of inhibitors. As well as acting as a reversible, competitive cholinesterase inhibitor, galantamine is an allosteric potentiator of neuronal nicotinic acetylcholine receptors (nAChR). Galantamine is a naturally occurring, tertiary alkaloid that was isolated originally from daffodil bulbs and is now synthesized commercially [Reminyl™ (Sanochemia; http://www.sanochemia.at)]. The mechanism of allosteric potentiation by galantamine in neuronal nAChRs has been extensively investigated using electrophysiological techniques. Positive modulation of submaximal agonist-induced current by galantamine takes place within a limited range of galantamine concentration (0.1–1.0 μM) [1]. Single-channel current measurement showed that galantamine potentiates agonist responses of nAChR by increasing the frequency of channel opening. Although cholinergic mechanism-based drugs ameliorate particular symptoms of Alzheimer's disease (AD), the extent to which these therapeutics affect the underlying causes that lead to neurodegeneration is not clear. Recent studies have made significant progress in



(i)

this area [2,3]. The intake of galantamine successfully reduced the deposition of extracellular clusters of β-amyloid plaques (thought to be one of the principal events in AD) in transgenic mice [2]. This activity was clearly linked to the interaction of galantamine with the nAChR rather than to its inhibition of cholinesterase. Similar studies undertaken with other acetylcholinesterase inhibitors (e.g. tacrine and physostigmine) were ineffective.

Studies performed in human neuroblastoma cells (SH-SY5Y) demonstrated that galantamine inhibits the neurotoxic aggregation of β-amyloid peptide (1–42), thus preventing apoptosis [3]. The neuroprotective effect of galantamine is concentration-dependent and the maximum effect is observed at a galantamine concentration of 300 nM. It is assumed that galantamine effects neuroprotection through upregulation of the expression of α7 neuronal nAChR (approximate twofold increase in protein expression) and the antiapoptotic protein Bcl-2 (approximate threefold increase in protein expression). However, the functional consequence of the upregulation in the receptor density caused by exposure to galantamine has not been investigated.

These two developments suggest that galantamine has a multi-faceted mode of action, in addition to enhancing cholinergic neurotransmission. Although cholinesterase inhibitor-based therapy provides symptomatic treatment, it does not cure AD. The pathology of AD involves many neurotransmitter systems, but cholinergic neurotransmission has the key role because this system can influence other receptors. The emerging propensity of galantamine to disrupt the two important hallmark symptoms of AD (amyloid aggregation and cholinergic dysfunction) make this molecule an interesting therapeutic candidate for AD that warrants further investigation.

1 Samochocki, M. *et al.* (2003) Galantamine is an allosterically potentiating ligand of neuronal nicotinic but not of muscarinic acetylcholine receptors. *J. Pharmacol. Exp. Ther.* 305, 1024–1036
2 Capsoni, S. *et al.* (2002) Nerve growth factor and galantamine ameliorate early signs of neurodegeneration in anti-nerve growth factor mice. *Proc. Natl. Acad. Sci. U. S. A.* 99, 12432–12437
3 Arias, E. *et al.* (2004) Galantamine prevents apoptosis induced by β-amyloid and thapsigargin: involvement of nicotinic acetylcholine receptors. *Neuropharmacology* 46, 103–114

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