Synthesis and radioactive labeling of galanthamine derivatives for examination of nicotinic acetylcholine receptor system

A.Schildan¹, R.Schirrmacher¹, A. Maelicke², F. Rösch¹

¹Institut für Kernchemie, ²Institut für Physiologische Chemie und Pathobiochemie, Johannes Gutenberg-Universität Mainz

The most commonly applied therapeutic approach to balance nicotinic cholinergic deficits in Alzheimer’s disease (AD) patients is the administration of acetylcholinesterase inhibitors (AChE-I) although they have been proven to be of limited therapeutic value. A novel approach to drug treatment in AD is the application of allosterically potentiating ligands (APL) acting on nicotinic acetylcholine receptors (nAChR). APLs interact with the receptor via binding sites that are distinct from those for nicotinic agonists and antagonists. They also up-modulate the channel activity of nAChRs in response to acetylcholine and other nicotinic agonists [1]. Representative members of this class of ligands are the plant alkaloids physostigmine, codeine, and galanthamine.

Galanthamine (Fig.1) acts as either an AChE-I or an APL (it also enforces receptor dependent neurotransmitter release on account of an unknown mechanism). The primary object of this work was to synthesise a galanthamine derivative which possesses only one of these properties, preferably acting as APL. These derivatives might be employed in PET studies and psychopharmacological examinations. Fig.2 shows the derivatives that have been synthesised and tested in vitro up to now.

Radioactive labelling of precursors 2 and 5 could easily be achieved by fluoroalkylation with 2-[¹⁸F]fluoroethyltosylate in DMF (2: 5 mg, 0.95 eq. 1 N NaOH, 20 min, 100°C; 5: 5 mg, 30 min, 140°C) in average radiochemical yields of 92% ([¹⁸F]3) and 31% ([¹⁸F]6) (referred to 2-[¹⁸F]fluoroethyltosylate, decay corrected). [³H]7 was synthesised by reaction of 1 with [³H]CH₃I (10 mCi, s.a. 80 Ci/mmol) in toluene (reaction conditions: r.t., 1 day) with a radiochemical yield of 62% (s.a. 54 Ci/mmol).