Acetylcholine receptors were classified in 1914 by Sir Henry Dale as muscarinic and nicotinic [1], where muscarinic receptors were selectively activated by muscarine and blocked by atropine. This simple definition has been modified as a result of molecular biological studies showing the existence of several muscarinic receptor subtypes [2–4]. Anticholinergic drugs antagonize the effects of acetylcholine at cholinergic postganglionic sites, designated muscarinic receptors. Muscarinic receptors are found on many different cell types and their presence on neurones, cardiac and smooth muscle cells, and exocrine, endocrine and paracrine cells [2–4] is of particular clinical importance.

Molecular cloning has defined five distinct muscarinic receptor subtypes with each subtype being encoded by distinct cellular genes. Muscarinic receptor sequences, m1–m5, encode the pharmacological receptor subtypes M1–M5 [2–4]. Pharmacologically, M1, M2 and M5 receptors are easily distinguished based on the selectivity of a panel of (largely) experimental antagonists. Moreover, there is distinct tissue distribution of these subtypes, with M1 receptors found in the CNS and stomach, M2 receptors on the heart and M3 receptors in CNS and on glandular tissue. M4 receptors have been found in brain NG108-15 neuroblastoma X glioma hybrid cells, rabbit lung and chicken heart and can be defined pharmacologically [5]. M3 receptors are also neuronal in origin [4]. Muscarinic receptors are examples of G-protein coupled receptors and structurally resemble all other members of this large family, possessing seven transmembrane spanning domains, with the third intracellular loop being the site of G-protein interaction. Second messenger coupling is subtype selective with M1, M3 and M5 coupling to phospholipase C to generate inositol-(1,4,5)triphosphate and M2 and M4 subtypes negatively coupled to adenylate cyclase to reduce the formation of cAMP [2–4,6]. Some of the characteristics of muscarinic receptor subtypes are illustrated in table 1.

Naturally occurring anticholinergic drugs such as atropine and hyoscine have been used in anaesthesia for more than a century, but glycopyrronium has been available only for the last 15 yr. Both atropine and hyoscine [7] are tertiary amines which cross the blood–brain barrier poorly and thus shows little in the way of central effects [8]. In this issue is an article by Gomez and colleagues [9] comparing the effects of atropine and glycopyrronium on M2 and M3 muscarinic receptor subtypes in the rat. The study tests the hypothesis (based on antischolergic and cardiac differences) that glycopyrronium may display different affinities for M2 (ventricle) and M3 (submandibular gland) subtypes. However, in a series of radioligand binding studies, no differences were found. This lack of selectivity of anticholinergic agents is a common problem and leads to the question: “Do these well defined muscarinic receptor subtypes have a place in clinical anaesthesia?”

Muscarinic receptors that control salivary and bronchial secretions are inhibited by lower doses of atropine (or hyoscine) than are necessary to inhibit receptors that regulate the effects of acetylcholine on the heart and eye [10]. With larger doses, the parasympathetic control of the urinary bladder and gastrointestinal tract are inhibited. However, larger doses are needed to inhibit gastric secretion and motility. As a result, a dose of atropine that inhibits gastric secretion of hydrogen ions invariably affects salivary secretion, heart rate, ocular accommodation and micturition. However, there are differences in the anticholinergic potency between drugs: hyoscine has a more potent action on the iris, ciliary body and secretory glands [11], conversely, atropine has greater anticholinergic effects at the heart, bronchial smooth muscle and gastrointestinal tract, and has a more prolonged action. Furthermore, in doses used clinically, atropine does not depress the CNS, as does hyoscine, which causes drowsiness, amnesia, fatigue and dreamless sleep with a reduction in rapid eye movement (REM) sleep [12]. Furthermore, there is evidence that anticholinergic drugs are not pure muscarinic receptor antagonists; notably the observation that small doses of atropine, hyoscine and glycopyrronium can produce slowing of the heart rate even when the drugs are administered in bilateral vagotomy [13]. This slowing of the heart rate reflects a weak, peripheral muscarinic receptor agonist activity. Previous speculation that slowing of the heart rate after administration of atropine was caused by a central vagal action is not supported by similar findings after administration of glycopyrro-
chloride also have direct antispasmodic effects. Conditions in which they have been used include peptic ulcer, irritable bowel syndrome and other gastrointestinal conditions associated with smooth muscle spasm [14]. However, adverse effects often limit their use. Benzhexol hydrochloride and benztrypine mesylate (tertiary amines) are used to treat extrapyramidal side effects of antipsychotic therapy [15] and antimuscarinic agents are used in the treatment of Parkinson’s disease, generally in the early stages when the condition is mild and often as adjunctive therapy to decrease excess salivation [16]. Antimuscarinics also have a potent bronchodilator activity and ipratropium by inhalation is commonly used to relieve bronchospasm, by acting on muscarinic receptors localized in the airway smooth muscle (probably M2), vascular endothelium, submucosal gland cells and neuronal structures [17].

Drugs commonly used by anaesthetists, such as the synthetic opioids derived from phenylpiperidine, fentanyl and pethidine, have been shown to bind to brain [18] and ileal [19] muscarinic receptors. The interaction of neuromuscular blocking agents with muscarinic receptors has been postulated by Riker and Wescoe [20]. Since then, several groups have shown that aminoesteroids block cardiac muscarinic receptors in doses similar to those required to produce neuromuscular block. Recently it has been shown that binding of the newer aminoesteroids to cardiac muscarinic receptors is complex [21] and further work is needed to define the nature of this complex interaction.

Muscarinic agonists are also used clinically. These drugs have a greater duration of action than acetylcholine because of their resistance to hydrolysis by plasma cholinesterase, anticholinesterase, or both. While these agents do not display subtype selectivity, they are devoid of significant nicotinic actions. Methacholine is rarely used clinically but bethanechol is used as a stimulant of the gastrointestinal tract smooth muscle and urinary bladder [22]. However, their side effects on other organ systems (glands, carotid and aortic bodies, respiratory system) make their clinical use difficult. Other cholinomimetic alkaloids such as pilocarpine, muscarine and arecoline have the same sites of action. Clinically pilocarpine, which has a predominant muscarinic action, when applied topically to the eye causes miosis, paralysis of accommodation and a sustained reduction in intraocular pressure [23].

Despite the existence of multiple subtypes, little progress has been made to target specific subtypes clinically. The majority of antimuscarinic agents used are relatively non-selective, except for pirenzepine (acting on M2 receptors in the stomach) which is used for the treatment of peptic ulcer. Is there a place for selective muscarinic antagonists in anesthesia? Evidently, most anaesthetists would find use for selective cardiac M1 muscarinic antagonists, in the prevention of “vagally-induced” bradycardia in ophthalmic or paediatric surgery. Also, anaesthetists might wish to use a selective M1 antagonist to decrease salivation during surgery, for example during neurosurgery or surgery in the prone position. Yet, in spite of detailed knowledge of muscarinic receptors at the molecular level, understanding of their functions, particularly in the CNS, lags behind. The cloning of genes encoding the different muscarinic receptor subtypes may provide new tools for the investigation and development of selective compounds for clinical use.

D. G. LAMBERT
B. L. APPADU
University Department of Anaesthesia
Leicester Royal Infirmary
Leicester LE1 5WW

References


