Muscarinic Receptors on Neurones of the Submucous Plexus*

R. A. North and A. Surprenant

The functions of the gastrointestinal epithelium are controlled by transmitters released from nerves. These nerves are of three main classes, corresponding to Langley’s (1921) divisions of the autonomic nervous system. First, sympathetic fibers reach the mucosa along the course of the blood vessels, passing directly through the enteric plexuses; however, a large number of sympathetic fibers end by making synaptic contacts with nerve cells of the submucous plexus and do not directly reach the mucosa (Costa and Furness 1984). Second, cholinergic nerves of the postganglionic part of the parasympathetic outflow innervate the mucosa. The cell bodies of these neurones constitute an unknown fraction of the neurones of the submucous plexus. Third, neurones intrinsic to the enteric nervous system, having their cell bodies in the submucous plexus, provide a dense projection to the mucosa. These cells are identified by their contents of cholecystokinin (CCK), neuropeptide Y (NPY), and the synthesizing enzyme for acetylcholine (ACh), choline acetyltransferase (ChAT) (for review, see Furness et al. 1984). Although the relative roles of the various types of innervation are not fully understood, it is well established that all three sets of nerves can under various circumstances have significant effects on secretory and absorptive activity (Gaginella and O’Dorisio 1979; Cooke et al. 1983; Tapper 1983).

Functional Properties of Neurones of the Submucous Plexus

The functional properties of the enteric nerve cells of the submucosa have been the subject of several studies (Hirst and McKirdy 1975; Hirst and Silinsky 1975; Surprenant 1984a; Surprenant 1984b; North and Surprenant 1985a; North and Surprenant 1985b; Mihara et al. 1985; for reviews, see North 1982; Surprenant 1986). In these electrophysiological studies, the projections and transmitter contents of the individual nerve cells are not known. However, the properties of the nerve cells of the guinea pig small intestine and cecum are rather uniform, with the exception of a small group (5%, AH cells) which are excluded from the present discussion. The 95% of submucous plexus neurones which have uniform properties might therefore be assumed to comprise both postganglionic parasympathetic cells and intrinsic enteric neurones lacking vagal input. It should be stressed that the relative number in each group is unknown. These neurones project not only to the mucosa, but they innervate each other extensively within the submucous plexus and send fibers to the myenteric plexus.

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The nerve cells of the submucous plexus receive three kinds of synaptic input. The fast excitatory postsynaptic potential (EPSP) is due to release of ACh, which acts within 1 ms on nicotinic receptors. This leads to a brief increase in conductance to both sodium and potassium ions, resulting in a net inward current through the subsynaptic membrane lasting for 1–2 ms. The charge thus accumulated on the inner face of the membrane capacitance the redistributes passively through the postsynaptic membrane, resulting in an EPSP typically lasting for 20–50 ms (Hirst and McKirdy 1975; Hirst and Silinsky 1975; Surprenant 1984a). This cholinergic fast EPSP is evoked by electrical stimulation of fibers running within the submucous plexus; the location of cell bodies of these fibers is not known. They may be in the vagal nuclei, in the myenteric plexus, or within the submucous plexus itself (Furness et al. 1984).

The second type of synaptic potential is the inhibitory postsynaptic potential (IPSP). This is evoked by electrical stimulation of the postganglionic sympathetic fibers as they enter the submucous plexus alongside the arterioles or as they run within the fiber strands of the plexus. These fibers release noradrenaline, which acts on the submucous plexus neurones to cause a prolonged opening (1–2 s) of membrane ion channels which allow only the passage of potassium ions. Potassium ions leave the cell because at resting potentials the forces acting on them by virtue of their concentration exceed the electrical forces holding them within the cell; the outward movement of potassium ions results in an increased negativity within the cell, a membrane hyperpolarization. The receptors on which noradrenaline acts to bring about the IPSP are of the α₂-subtype (North and Surprenant 1985 a). There is little doubt that the noradrenaline is released from sympathetic fibers firstly because there are no noradrenaline-containing cells intrinsic to the guinea pig small intestine and secondly because the IPSP is abolished by extrinsic denervation (Surprenant 1984a).

The third synaptic potential is the slow EPSP (Surprenant 1984a; Mihara et al. 1985). The transmitter (most likely substance, P) released from the presynaptic nerves acts on receptors on the submucous neurones; the result of this is the closure of some potassium channels in the membrane which are normally open at the resting membrane potential. The closure of these potassium channels allows the membrane potential to move towards the equilibrium potentials for the other ions to which it is permeable, predominately sodium. This causes a membrane depolarization (slow EPSP). Both the IPSP (1–2 s) and the slow EPSP (5–30 s) are long-lasting synaptic potentials, the time course of which probably results from slow changes in the level of an intracellular second messenger which is triggered by the interaction between the transmitter and its cell surface receptor. The origin of the presynaptic fibers that give rise to the slow EPSP is not certain but is presumed to be largely the other neurones of the enteric plexuses, or perhaps vagal fibers.

There is indirect evidence from experimental work involving other parts of the gastrointestinal tract for muscarinic cholinergic transmission onto cells of the submucous plexus (Pagani et al. 1984). Ach is known to mediate a slow EPSP by acting on muscarinic receptors in a variety of autonomic neurones (see North 1985), and the time course and ionic mechanism of that synaptic potential is very similar to that observed for the peptide-mediated slow EPSP in the submucous plexus. Such muscarinic potentials occur in the myenteric plexus (North and Tokimasa 1982) but