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Two modes of action of ganglionic blocking drugs

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Non-depolarizing ganglion blocking drugs are usually thought to block acetylcholine receptors competitively, though Blackman (1959) suggested that hexamethonium acts by blocking ionic channels rather than by competition.

We have used a two microelectrode voltage clamp technique on rat submandibular ganglion cells (Ascher, Large & Rang, 1978) to investigate the actions of blocking drugs in more detail.

With the membrane potential held constant application of carbachol (by perfusion or microiontophoresis) causes an inward current whose magnitude increases markedly with hyperpolarization. Some antagonists (trimetaphan, 2.5μM; surugatoxin, 0.2 μM) reduce the carbachol-induced current equally at all membrane potentials (i.e. the block is not voltage-dependent). Others (tubocurarine, 5 μM; hexamethonium 2 μM; decamethonium, 50 μM) reduce the current proportionately more as the membrane is hyperpolarized (voltage-dependent block). Defining Λ as the ratio of current in the absence and in the presence of antagonist, voltage dependence can be expressed as $(\Lambda_{-80}-1)/(\Lambda_{-50}-1)$ where the subscript represents membrane potential. Values obtained were: trimetaphan 1.18, surugatoxin 0.86, tubocurarine 3.13, hexamethonium 3.17, decamethonium 2.87. Marked voltage dependence suggests, but does not prove, a mechanism other than competitive block.

With competitive block $\Lambda-1$ should decrease as the agonist concentration is increased. We tested this by measuring $(\Lambda_{large}-1)/(\Lambda_{small}-1)$ with alternate large and small responses to iontophoretically applied carbachol, differing 3–4 fold in amplitude. With trimetaphan this ratio is slightly less than one; with voltage-dependent antagonists this ratio ranges from 1.3 to 1.7, which is not consistent with competitive block.

This pattern of block increasing with agonist concentration and with membrane potential favours a channel block mechanism such as that described for procaine and other agents at the neuromuscular junction (Adams, 1977; Feltz, Large & Trautmann, 1977, Neher & Steinbach, 1978) and for various acetylcholine antagonists on Aplysia neurones (Ascher, Marty & Neild, 1978).

Kinetic studies were carried out with voltage jumps, in which the change of current with time was followed after a step in membrane potential from −50mV to −80mV. With carbachol alone the current increases to a new level within 10 ms (the limit of resolution of our voltage clamp) and no relaxation is detectable. With hexamethonium or tubocurarine present, the current increases rapidly and then decreases exponentially with a time constant of 1–2 s. This relaxation becomes faster if the antagonist concentration is increased, as expected for a slowly-dissociating channel blocker. With decamethonium the slow relaxation is in the opposite direction and becomes slower if the decamethonium concentration is increased, as predicted for a rapidly dissociating channel blocker (Adams, 1977, Ascher, Large & Rang, 1978).

It is concluded that tubocurarine, hexamethonium and decamethonium act mainly or entirely by blocking ionic channels, whereas trimetaphan and surugatoxin probably block receptors.

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