The action of acetylcholine and other drugs on the efflux of potassium and rubidium from smooth muscle of the guinea-pig intestine

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Commentary by

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Most studies of muscarinic receptors up to this time (and many subsequently) had relied on the contractile responses of smooth muscle. This paper introduced a rather elegant method of evaluating responses by measurement of potassium efflux. Good quantitation could be achieved for both agonists and antagonists but surprisingly the potency of agonists for the efflux response was quite different from that for the contractile response except in the case of partial or very weak agonists. Even more astonishing, the structure activity for agonists for the two responses were strikingly different. However, the sensitivity of the two responses to antagonists were identical as were the estimates of spare receptors.

We had the curious situation in which the antagonists provided clear evidence that both responses were due to a single receptor and the contrary evidence from the agonist data that suggested distinct receptors for efflux and contraction. How could this paradox be resolved? No satisfactory explanation could be offered, although it was hinted that perhaps there might be subtypes of muscarinic receptor (the first real evidence for subtypes of muscarinic receptors was not obtained until 12 years later with the evaluation of pirenzipine (Hammer *et al*, 1980).

A further study (Burgen & Spero, 1970) showed that the contractile response was very sensitive to the ionic composition of the bathing fluid whereas the efflux was not at all sensitive. In some ionic combinations the difference in agonist selectivity virtually disappeared. This led to the suggestion that in some way the difference was related to the coupling process between the receptor and the responses.

However, the answer to the paradox came with studies of antagonist and agonist binding to the receptor using radioligands. These showed that binding of antagonists fitted simple mass action functions and gave binding constants in excellent agreement with those deduced from measurements on smooth muscle (Hulme *et al*, 1978). In contrast, agonists did not give simple mass action binding curves, but rather flat or inflected curves. Evidence was produced that this was due to the presence of at least two states of the receptor, high and low (a smaller amount of a super high state was also detected) differing strikingly in affinity for various agonists (Birdsall *et al*, 1978). It looked as though this could provide the explanation for our paradox with contraction being coupled to the high affinity form and flux to the low affinity form. This remains the most satisfactory conclusion and this paper is an illustration of the not uncommon circumstance in science that a new method uncovers an unexpected phenomenon whose elucidation needs yet further new approaches.

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