The action of morphine and related substances on contraction and on acetylcholine output of coaxially stimulated guinea-pig ileum

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Commentary by

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These introductory comments were to have been written by Hans Kosterlitz. That would have been an account by someone contemporaneously involved in the problem of acetylcholine release from autonomic nerves and someone who was later to use the approach described in this paper to detect and eventually identify the enkephalin transmitters in the brain. Hans's final illness made that impossible and these comments less adequate as a result.

Paton's paper is written with his usual clarity, describing convincing experiments in support of his conclusions; morphine and its relatives inhibit the release of acetylcholine from post-ganglionic nerve endings in the guinea-pig ileum, they do so with a reasonable relationship to their analgesic potency and the reduction in the muscle response is consistent with the reduction in transmitter release. Today it is difficult to avoid the mental addition of, "as a result of binding to opiate receptors" but such a suggestion appears nowhere in the paper nor do I believe Paton would have considered it as a possibility. The concept of pre-synaptic receptors is so familiar, the receptor populations so extensive and so much is known even of their mode of action, that it is difficult to empathise with the difficulty then to conceive of such a possibility. Nevertheless in 1957 such as idea would have been quite foreign. Indeed many believed there was good reason for *not* having receptors on terminals since this helped to ensure unidirectional transmission at synapses. On this view nerve endings released transmitter as a result of an electrical event, depolarisation by the action potential, but had no receptors and therefore retrograde excitation was not possible. The post-synaptic cells, nerve or effector, had receptors and so could produce a response to the released transmitter but were unable to respond to the electrical currents from the much smaller nerve endings. This view was to change when the simple technique described here of measuring directly the release of transmitter was used to show that morphine inhibition of release was completely reversed by the selective morphine antagonist naloxone (Henderson *et al*, 1972). The concept was confirmed and greatly strengthened by the subsequent demonstration by Snyder (1975) of the selective localisation and binding of opiates in the brain.

Though for Paton in 1957 the idea of drug receptors on nerve endings was perhaps a bridge too far his interest in the factors controlling drug release may have alerted him to another possibility requiring selective drug binding at nerve endings, noradrenaline re-uptake by adrenergic nerves. This suggestion was made in the discussion following the paper given by G.L. Brown at a Ciba symposium in 1960 on the ability of high stimulation frequencies and the α-receptor blocking drug phenoxybenzamine to increase the recovery of noradrenaline. This G.L. attributed to the ability of high frequencies to saturate post-synaptic receptors and phenoxybenzamine to block these receptors which he believed were involved in the destruction of the transmitter. Paton's alternative and correct explanation was that these conditions prevented the re-uptake of noradrenaline back into the nerve endings, an explanation described at the time by G.L. as "heretical". In the following years re-uptake of radioactive noradrenaline was beautifully demonstrated by Hertting *et al* (1961).

As to the subsequent significance of this paper I think most would agree it lies with the work of Kosterlitz's group on the enkephalins. First the

demonstration of a morphine-like inhibitory substance in brain extracts and their subsequent isolation, separation and identification as the simple pentapeptides Met- and Leu-enkephalin (Hughes *et al* 1975). This was followed by studies of the differential effect of various opiates on the guinea-pig ileum and mouse vas deferens leading to the identification of the different opiate receptors.

It is never easy to anticipate the future importance of new information and I believe this work was probably regarded at the time as simply another study on the old problem of morphine's action whose greatest value might be in providing a useful *in vitro* screen for morphine-like analgesic action. This thought was prompted by my difficulty in getting a copy of the paper when I found myself in the inevitable last minute rush to produce these comments. When G.L. died I inherited his extensive collection of reprints among which were, I believed, most of the papers by his long time friend Bill Paton. When I came to search, the only paper among many by Paton which was missing was "The action of morphine——on the guinea-pig ileum!

References

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