Actions of triethylcholine on neuromuscular transmission

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Commentary by

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During an investigation of the anticholinesterase activity of a series of bisphenacyl derivatives, Schueler and his colleagues in New Orleans had found, in the mid 1950s, that one of them (later called hemicholinium No 3, HC-3) was virtually devoid of anticholinesterase activity but exhibited an unusual form of delayed paralysing activity in mice. The molecule contained two choline-like moieties and it underwent hemiacetal formation in solution; hence the name "hemicholinium" coined by Schueler. Later work, much of which was reviewed by Bowman & Marshall (1972) and MacIntosh & Collier (1976), showed that HC-3 acts by competing with choline for transport into cholinergic nerve endings. It thereby deprives the nerve endings of the choline needed for acetylcholine synthesis, and so an important component of its blocking action is pre-junctional in origin. Characteristically its blocking action is slow in onset and dependent on a high frequency of nerve impulses; its inhibitory action on choline transport is overcome by an excess of choline. Although it enters the axoplasm, HC-3 cannot be released by nerve impulses (Collier, 1973).

For different reasons, Michael Rand and I came together for this study on the triethyl analogue of choline, which we called "triethylcholine" or TEC; more strictly it is [triethyl(2-hydroxyethyl)ammonium]. We had each been interested in HC-3. Rand's interest stemmed from his need for pharmacological tools in testing the Burn & Rand hypothesis that acetylcholine was a co-transmitter in noradrenergic nerves, the so-called cholinergic-link hypothesis which is referred to elsewhere in this volume. I was interested in various kinds of drugs that blocked neuromuscular transmission, and HC-3, though potent, was too mixed in its actions, having both pre- and post-junctional (curare-like) blocking actions.

Keston & Wortis (1946) had shown that the respiratory paralysis in mice produced by TEC was reversed by choline, and Burgen *et al* (1956) had found that the compound is acetylated by choline-O-acetyltransferase about as effectively as choline itself. After the experiments described in the paper here commented upon, together with others (mostly reviewed in Bowman, 1990), we proposed that TEC, having been transported into the axoplasm, was there acetylated, loaded into vesicles, and then released by nerve impulses as an active "false transmitter". This notion was later confirmed both by our own group, especially Brian Hemsworth, and by others. TEC has relatively much less post-junctional "curare-like" action that has hemicholinium but it has a weak post-synaptic ganglion-blocking action. It also has a weak ability, initially, to facilitate acetylcholine release from nerve endings, probably because of a K^+-channel blocking action resembling that of the tetraethylammonium ion.

Kopin (1968) at NIH defined the criteria for designating a substance as a false transmitter. He always credited us with first having thought of the concept, and we were willing enough to accept the accolade. In retrospect, however, I rather believe that Arnold Burgen preceded us with the suggestion. Perhaps we simply made more of a song and dance about it.

Michael Rand and I were of the opinion that a drug of the TEC-type (TEC being thought of as a starter compound) might be of use in the therapeutic control of localised muscle spasticity of the kind that is maintained by an abnormally high discharge of nerve impulses, the high traffic of nerve impulses and consequent demand for acetylcholine, itself leading to failure of transmission in the presence of such a drug. Laurence & Webster (1961) were good enough to test the idea in rabbits with unilateral tetanus (induced by *Cl. tetani*). The

spasms in the affected limbs were relieved without impairing normal movement including breathing. Unfortunately, when tested in human patients with localised spasticity, there was no beneficial effect at all. We are of the opinion that the patients selected for the tests were unsuitable in that their spasticity was of such long-standing that muscle shortening or contracture had developed which was no longer maintained by nerve impulses. It remains possible therefore that a drug of this type might be found of value in the relief of localized muscle spasticity of the appropriate kind.

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