Convulsant substances as antagonists of GABA and presynaptic inhibition in the cuneate nucleus

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The convulsant substances bicuculline, picrotoxin and (+) tubocurarine were previously reported to be γ-aminobutyric acid (GABA) antagonists when applied by micro-iontophoresis in the cat cuneate nucleus (Hill, Simmonds & Straughan, 1973a). In similar experiments on cats anaesthetized with halothane/N_2O in oxygen and prepared as before (Hill *et al.*, 1973b) three other convulsants, penicillin G, leptazol and bemegride, have also been examined as GABA antagonists. Penicillin G was found to be only a weak GABA antagonist and it was not possible to demonstrate any antagonism with leptazol or bemegride, comparisons being made by the method of Hill & Simmonds (1973).

In further experiments, leptazol and bemegride were infused intravenously into cats whilst measuring the amplitude of the P-wave recorded from the surface of the cuneate nucleus in response to stimulation of a paw (Andersen, Eccles, Schmidt & Yokata, 1964). This P-wave amplitude is generally accepted as an index of presynaptic inhibition. Leptazol and bemegride in subconvulsant doses readily reduced the P-wave in a similar manner to bicuculline and picrotoxin (Hill *et al.*, 1973c) without antagonizing responses to micro-iontophoretically applied GABA. The other convulsants studied were not given intravenously, as their charge structure prevents significant amounts accumulating in the CNS.

To circumvent this latter problem, drugs were applied topically to the cuneate nucleus of rats anaesthetized with urethane and prepared as described previously (Hill & Miller, 1974). Presynaptic inhibition was assessed as in the cat experiments. Picrotoxin, (+) tubocurarine and penicillin G were applied as neutral solutions in saline and all were found to reduce P-wave amplitude in a similar manner.

Although precise potency comparisons are difficult, especially when data must be extrapolated from micro-iontophoretic experiments, it was clear that a variety of convulsant drugs, only some of which could be shown to be GABA antagonists, would produce striking reductions in presynaptic inhibition as judged by P-wave amplitude. These amplitude changes provide a sensitive index of the action of many convulsant drugs since they precede and correlate with the development of electrographic seizures. However, the mechanism by which drugs alter the P-wave still needs further elucidation. If GABA is the inhibitory neurotransmitter at both pre- and postsynaptic sites in the mammalian cuneate nucleus then the reasons why the presynaptic receptors are much more readily blocked than the postsynaptic receptors by a variety of convulsant agents needs to be discovered.

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