The effect of some anticonvulsant drugs on leptazol and bicuculline induced acetylcholine efflux from rat cerebral cortex

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It is known that cerebral stimulant drugs increase the efflux of acetylcholine (ACh) from the cerebral cortex (Hemsworth & Neal, 1968), but the effect of anticonvulsant drugs has not been studied. We have investigated the effect of three anticonvulsant drugs; phenytoin, trimethadione and phenobarbitone, on convulsive activity and ACh release induced by leptazol and bicuculline.

ACh was collected in cups, containing 1 ml Locke solution, placed on the cerebral cortex of rats anaesthetized with urethane (1·3–1·8 g/kg I.P.), and assayed on the dorsal muscle of the leech. The e.e.g. was recorded from an epidural screw electrode in the skull, on the opposite side to the cup. Convulsive activity was recorded from a piezoelectric strip strapped to a forepaw. Both recordings were integrated and counted to give a quantitative measure. Body temperature was maintained at 37° C as slight fluctuations were found to modify both e.e.g. activity and ACh efflux. Leptazol experiments demonstrated a close correlation between induced e.e.g. activity and ACh release and the latter was shown to be calcium dependent.

Intraperitoneal or intravenous leptazol produced a dose dependent increase in ACh efflux proportional to e.e.g. activation and convulsive activity. A single intraperitoneal injection (250 mg/kg) produced a twelve-fold increase in ACh efflux together with convulsive e.e.g. activation. This response provided a suitable baseline for the study of anticonvulsant drugs. Bicuculline (1·25 mg/kg I.V.) produced a seven-fold increase in ACh efflux related to e.e.g. and convulsive activity, but this effect lasted only 20–30 minutes. A suitably maintained baseline for the study of anticonvulsant drugs was achieved, however, with a slow intravenous infusion (12 μg/min).

Leptazol induced convulsive activity, e.e.g. activation and ACh release were reduced by trimethadione (ED50, 212 mg/kg I.P.) whilst phenytoin (20–50 mg/kg I.V.) produced no significant reduction, large doses tending to accentuate all the recorded parameters. In contrast, phenobarbitone reduced leptazol induced e.e.g. and convulsive activity ED50, 33 mg/kg I.P.) but left the ACh release relatively unaffected. This would be explicable if phenobarbitone produced a selective depression of cerebral cholinoceptive neurones as suggested by observations of Bradley & Dray (1972) on brain stem neurones during barbiturate anaesthesia. However, we have been unable to show any reduction by this dose of phenobarbitone of e.e.g. activation and muscle movements induced by topical eserine (5×10^{-3} g/ml).

When tested against bicuculline seizures, e.e.g. activation and ACh release the three anticonvulsants showed some differences in activity compared with their effects against leptazol. Trimethadione again reduced both the e.e.g. activity and ACh release but was only half as active as against leptazol. Phenytoin did not reduce either parameters significantly, as before. Phenobarbitone reduced e.e.g. activity almost to the same extent as against leptazol but the reduction of ACh release appeared more marked. These differential effects of phenobarbitone are being studied further.

C. R. G. is an M.R.C. scholar.

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