Assessment of the anticonvulsant activity of inhibitors of high-affinity GABA uptake

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The post-synaptic action of the inhibitory transmitter GABA may be terminated by the high-affinity uptake processes which have been shown to exist in the CNS (Iversen & Neal, 1968; Krogsgaard-Larsen, Johnston, Curtis, Game & McCulloch, 1975). Inhibitors of GABA uptake might therefore be expected to potentiate the action of GABA released from inhibitory nerve terminals and so possess depressant or anti-convulsant properties, although no reports of this have appeared in the literature. We have investigated the actions of various uptake blockers on the characteristic running fits and convulsions induced by 3-mercaptopropionic acid (3-MP), which acts by specifically inhibiting glutamate decarboxylase (Lamar, 1970) thereby reducing the rate of GABA synthesis (Adcock & Taberner, 1977) and, eventually, the total brain GABA level (Karlsson, Fonnum, Malthe-Sorensen & Storm-Mathisen, 1974).

Female LACG mice were injected i.p. with varying doses of 3-MP 15 min after the intracerebroventricular injection of 2 μmoles of the GABA uptake inhibitors L-2,4-diaminobutyric acid (DABA), nipecotic acid or *cis*-1,3-aminocyclohexane carboxylic acid (ACHC) in 5 μl of 20 mM sodium phosphate buffer, pH 7.4. The ED_{50} for running fits and CD_{50} for full tonic clonic convulsions were determined from the proportion of animals showing these symptoms using the moving average interpolation method of Weil (1952).

3-MP given alone had an ED_{50} of 37.7 ± 1.15 mg/kg ($\pm$95% confidence limits) and a CD_{50} of 42.5 ± 1.09 mg/kg. Following the DABA pretreatment the ED_{50} was raised to 57.5 ± 1.12 mg/kg and the CD_{50} to 100.5 ± 1.15 mg/kg. Following the nipecotic acid pretreatment the ED_{50} was 34.5 ± 1.08 mg/kg and the CD_{50} 46.6 ± 1.15 mg/kg. ACHC had no anticonvulsant activity and tended to produce an increase in activity in the mice. GABA also had no anticonvulsant activity at the same dose level although it produced short-term sedation and, when given simultaneously with 3-MP, slightly increased the latency to running fits and convulsions. DABA produced a marked reduction in the spontaneous activity of the mice lasting between 60 and 90 min post injection.

In conclusion, it is suggested that the use of 3-MP induced running fits and convlusions may provide a useful tool for the examination of potential anticonvulsant activity particularly in compounds which interfere with the GABA system. Using the 3-MP in this study it has been possible to show that DABA has potent anticonvulsant properties whereas nipecotic acid and ACHC have negligible activity. This difference may be due to DABA having some property not related to its antagonism of GABA uptake, or be related to differences in metabolism and distribution, or their relative effectiveness at blocking GABA uptake into neurons and glia (Bowery, Jones & Neal, 1976).

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Referemces

ADCOCK, T. & TABERNER, P.V. (1977). Measuring changes in cerebral glutamate and GABA metabolism prior to convulsions induced by 3-mercaptopropionate. *Biochem. Pharmac.* (in press).

BOWERY, N.G., JONES, G.P. & NEAL, M.J. (1976). Selective inhibition of neuronal GABA uptake by *cis*-1,3-aminocyclohexane carboxylic acid. *Nature, Lond.* **264**, 281–284.

IVERSEN, L.L. & NEAL, M.J. (1968). The uptake of (^{3}H)-GABA by slices of rat cerebral cortex. *J. Neurochem.* **15**, 1141–1149.

KARLSSON, A., FONNUM, F., MALTHE-SORENSSEN, D. & STORM-MATHISEN, J. (1974). Effect of the convulsive agent 3-mercaptopropionic acid on the levels of GABA, other amino acids and glutamate decarboxylase in different regions of rat brain. *Biochem. Pharmac.*, **23**, 3053–3061.

KROGSGAARD-LARSEN, P., JOHNSTON, G.A.R., CURTIS, D.R., GAME, C.J.A. & McCULLOCH, R.M. (1975). Structure and biological activity of a series of conformationally restricted analogues of GABA. *J. Neurochem.*, **25**, 803–809.

LAMAR, C. (1970). Mercaptopropionic acid: a convulsant that inhibits glutamate decarboxylase. *J. Neurochem.* **17**, 165–170.

WEIL, C.S. (1952). Tables for convenient calculation of median-effective dose (LD_{50} or ED_{50}) and instructions in their use. *Biometrics*, **8**, 249–263.