Effects of sodium valproate and ethanolamine-*o*-sulphate on GABA metabolism *in vivo*

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Sodium *n*-dipropylacetate (valproate, Epilim) is an effective anticonvulsant which appears to act by raising brain GABA levels (Lacolle, Ferrandes & Eymand, 1978), although it is only a weak inhibitor of GABA aminotransferase (GABA-T) and may act indirectly by inhibiting succinic semialdehyde dehydrogenase or aldehyde reductase (Whittle & Turner, 1978). In this study the effects of valproate on GABA metabolism in mouse striatum *in vivo* have been compared with ethanolamine-O-sulphate (EOS) a specific inhibitor of GABA-T which also raises the brain GABA concentration and is anticonvulsant (Baxter, Fowler, Miller & Walker, 1973).

Adult LACG mice of either sex were used throughout. EOS was prepared by the methods of Lloyd, Tudball & Dodgson (1961) and administered intracerebroventricularly (ICV) in 5 µl of isotonic buffered saline (pH 7.4). Control mice received the same volume of vehicle. GABA metabolism was measured by injecting 5 µCi of D-[U-^{14}C]-glucose ICV and determining the relative incorporation of [^{14}C] into glutamate and GABA after 4 min following the procedures described previously (Marigold & Taberner, 1978).

EOS (0.4 µmole) did not significantly alter the relative incorporation of [^{14}C] into glutamate and aspartate at 12, 24 or 48 h after injection, although incorporation into GABA was increased by 30–60% above control at 12 and 24 hours. Valproate (0.54 mmole/kg i.p.) slightly reduced the incorporation of [^{14}C] into glutamate and increased that into GABA at 60 and 90 min after injection. At these time intervals there was no measurable anticonvulsant activity against 3-mercapto-propionic acid-induced running fits and the mice appeared behaviourally normal, with no evident sedation or reduced reactivity. At 60 min after valproate (1.08 mmoles/kg) the CD_{50} of 3-mercaptopropionic acid was increased from 0.325 ± 0.010 to 0.442 ± 0.012 mmoles/kg i.p. (±95% confidence limits), but no significant increase in the incorporation of [^{14}C] into GABA was observed, although the mice appeared sedated.

It has previously been shown that reversible enzyme inhibitors can affect the relative incorporation of [^{14}C] into glutamate and GABA *in vivo* at doses below those required to produce measurable changes in either glutamate decarboxylase or GABA-T activity. In the case of valproate, however, there is no significant evidence of a relative increase in GABA synthesis or reduction in GABA breakdown at a time when marked anticonvulsant activity can be observed. At doses above 1.2 mmoles/kg i.p. valproate does affect GABA metabolism and raise brain GABA levels, but this mechanism may not be responsible for the anticonvulsant action of the drug.

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Anticonvulsant properties of ethyl-*N*-phthalimidoxy acetate

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Despite recent reports by some workers to suggest that γ-aminobutyric acid (GABA) may have excitatory action in some areas of the vertebrate central nervous system (CNS) (De Groat 1970; De Groat, Lalley & Block 1971), this transmitter is usually regarded as serving an inhibitory function in the CNS. High brain levels of GABA protect many animal species against various types of seizures while low levels lead to seizures (Eidelberge, Baxter, Roberts, Saldias, & French, 1960; Kuriyama, Roberts, & Rubenstein, 1966). Since GABA itself does not penetrate the CNS in appreciable quantities, however, in-