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

P.V. TABERNER

Department of Pharmacology, Medical School, University of Bristol, Bristol BS8 1TD

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.

References

BAXTER, M.G., FOWLER, L.J., MILLER, A.A. & WALKER, J.M.G. (1973). Some behavioural and anticonvulsant actions in mice of ethanolamine-*o*-sulphate, an inhibitor of 4-aminobutyrate aminotransferase. *Br. J. Pharmac.* **47**, 681P.

LACOLLE, J.Y., FERRANDES, B. & EYMARD, P. (1978). Profile of anticonvulsant activity of sodium valproate. Role of GABA. In: "*Advances in Epileptology—1977*". Meinardi, H. & Rowan A.J. (Eds.). Swets & Zeitlinger, B.V. Amsterdam. p. 162–167.

LLOYD, A.G., TUDBALL, N. & DODGSON, K.S. (1961). Infrared studies on sulphate esters. III. O-sulphate esters of alcohols, amino alcohols and hydroxylated acids. *Biochim. Biophys. Acta* **52**, p. 413–419.

MARIGOLD, J. & TABERNER, P.V. (1978). The effects of allylglycine on GABA synthesis *in vivo*. *Biochem. Pharmac.* **27**, p. 1109–1112.

WHITTLE, S.R. & TURNER, A.J. (1978). Effects of the anticonvulsant sodium valproate on γ-aminobutyrate and aldehyde metabolism in ox brain. *J. Neurochem.* **31**, 1453–1459.

Anticonvulsant properties of ethyl-*N*-phthalimidoxy acetate

G.D. LAHAN, G. OSUIDE & F. STANSFIELD

Department of Pharmacology, Faculty of Pharmaceutical Sciences and Department of Chemistry, Faculty of Science Ahmadu Bello University, Zaria, Nigeria

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-

direct methods have been employed for causing its elevation in the brain. Notable among these methods is the use of aminooxyacetic acid, AOAA, a potent GABA-transaminase enzyme inhibitor but this compound possesses convulsant properties at high doses (Wallach, 1961; Osuide, 1972). In this experiment, we have therefore investigated an analogue of AOAA namely ethyl-*N*-phthalimidoxy acetate (ENPA) for anticonvulsant properties among other studies.

Experiments were performed on young male Warren chicks weighing 35–50 g and adult male albino rats weighing between 150–230 g. Maximal electroshock was delivered, via steel electrodes, using the Ugo Basile ECT unit model 7801. Chemical convulsions were induced with strychnine, and leptazol, injected intraperitoneally. Results from electroshock experiments were compared with phenytoin while troxidone was used as our standard drug for comparing results from strychnine- and leptazol-induced seizure experiments.

ENPA (100 mg/kg) offered a complete protection against ECT in chicks when administered i.p. 5–6 h before electroshock. It thus proved more potent than phenytoin which was able to offer approximately 60% protection under similar conditions. It was equipotent with troxidone in offering total protection against doses of strychnine and leptazol which produced 60% convulsions and 10–20% lethality in chicks. ENPA was inferior to AOAA in its anticonvulsant effects but was completely devoid of convulsant properties even at doses many times higher than convulsant doses of AOAA. It is thought that the blocking of the amino group in such a way as to make hydrolysis, *in vivo*, difficult was to a large extent accountable for the elimination of convulsant actions of AOAA. Measurement of brain GABA levels following ENPA administration showed that GABA levels were greatly elevated during the period of peak anticonvulsant activity. This probably contributed immensely to the observed anticonvulsant property.

References

DEGROAT, W.C. (1970). The actions of gamma-aminobutyric acid and related amino acids on mammalian autonomic ganglia. *J. Pharmac. exp. Therap.* **172**, 384–396.

DEGROAT, W.C. LALLEY, P.M. & BLOCK, M. (1971). The effect of bicuculline and GABA on the superior cervical ganglion of the cat. Brain Res. **25**, 665–668.

EIDELBERGE, E., BAXTER, C.F., ROBERTS, E., SALDIAS, C.A., & FRENCH, J.D. (1960). Anticonvulsant properties of hydroxylamines and elevation of cerebral GABA in cats. (25106). *Proc. Soc. expt. Biol. Med.* **101**, 815–817.

KURIYAMA, K., ROBERTS, E., AND RUBENSTEIN, M.K. (1966). Elevation of gamma-aminobutyric acid in brain with amino-oxyacetic acid and susceptibility to convulsive seizures in mice. A quantitative re-evaluation. *Biochem. Pharmac.* **15**, 221–236.

OSUIDE, G. (1972). Pharmacological properties of amino-oxyacetic acid in the chicken. *Br. J. Pharmac.* **44**, 31–44.

WALLACH, D.P. (1961). Studies on the GABA pathway-I: The inhibition of gamma-aminobutyric acid- -ketoghltaric acid transaminase *in vitro* and *in vivo* by U-7524 (amino oxyacetic acid). *Biochem. Pharmac.* **5**, 323–331.

Biphasic effect of direct GABA mimetic drugs on haloperidol-induced catalepsy

K.G. LLOYD, M.T. WILLIGENS & P. WORMS

Department of Neuropharmacology, Synthélabo-L.E.R.S., 31, ave P.V. Couturier, F 92220 Bagneux, France

γ-Aminobutyric acid (GABA) is involved in the regulation of dopaminergic neuron activity within the forebrain. This includes direct inhibitory and indirect excitatory effects of GABA on the nigrostriatal DAergic pathway and also regulation of DA transmission by striatal GABA interneurons (Bartholini & Stadler, 1977; Lloyd, 1978). We have recently reported that GABA-mimetic drugs potentiate neuroleptic-induced catalepsy (Worms, Willigens & Lloyd, 1978). Such an effect was interpreted as evidence for the inhibitory action of GABA on nigro-striatal DA neurons. However, low doses of GABA antagonists potentiated and high doses antagonized haloperidol-catalepsy supporting the interaction of two GABA receptors with the DA neurons.

In the study reported here, male Sprague Dawley rats (CD COBS, Charles River, France) weighing 200 to 250 g were used. Catalepsy measurements (4-cork test) were performed as described previously (Worms *et al.*, 1978). Drugs were injected i.p. simultaneously with- (SL 76 002, muscimol) or 2 h prior to- (AOAA, γ-acetylenic GABA: GAG) halopéridol (0.6 mg/kg i.p.).

Muscimol and SL 76002 ([α-(chloro-4'-phenyl) fluoro-5-hydroxy-2-benzylidene amino]-4-butyramide) caused a biphasic effect, first decreasing at low doses and then potentiating at higher doses the haloperidol-mediated catalepsy (Muscimol: 42% and 137% of haloperidol treated animals at 0.25 and 2 mg/kg, respectively; SL 76002; 50% and 138% of haloperidol treated animals at 12.5 and 100 mg/kg, respectively. $P < 0.01$ vs haloperidol alone in all cases). In contrast, administration