The buccal absorption of some β-adrenoceptor blocking drugs

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The buccal absorption of four β-adrenoceptor blocking drugs was studied over a pH range of 5·5–9·5, using the method of Beckett & Triggs (1967). The test was made on two subjects for each of the four drugs; propranolol HCl and practolol (ICI Ltd.); pindolol (LB 46, Sandoz Ltd.) and Ro 3-3528 (6-7-dimethyl-α-[isopropylamino-methyl]-2-benzofuranmethanol hydrochloride, Roche Products Ltd.) but intrasubject comparisons were used because of the variation between individuals (Beckett & Triggs, 1967).

The partition coefficient between 0·1 N NaOH and chloroform was determined for each drug. At this pH each of the compounds was completely undissociated, the pKa values being propranolol, 9·45; practolol, 9·50; pindolol, 9·30 and Ro 3-3528, 9·25. Information on the solubility of each of the drugs in water was provided by the relevant pharmaceutical companies. The partition coefficient and water solubility at 20° C were respectively, propranolol, 28·5 and 5%; practolol, 0·19 and 0·25%; pindolol, 0·45 and 0·012% Ro 3-3528, 14·7 and 2%.

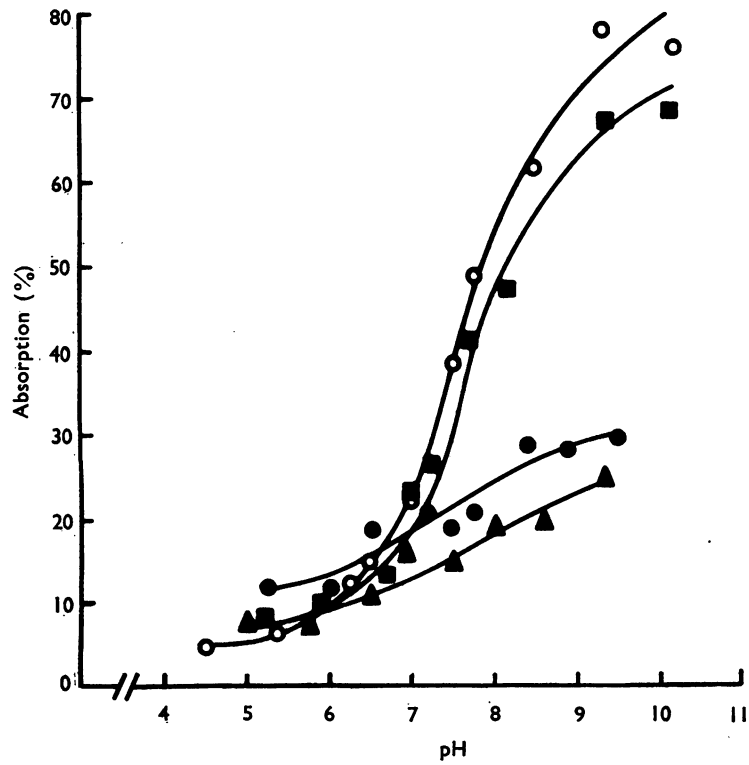

FIG. 1. Buccal absorption of propranolol, ○; Ro 3-3528, ■; pindolol, ●; and practolol, ▲, at varying pH.

Figure 1 shows an apparent relation between the water solubility and partition coefficient of the drugs and the extent of their absorption through or adsorption onto (Dearden & Tomlinson, 1971) the buccal mucosa. This situation is not reflected in the extent or rate of intestinal absorption of the drugs. All four are 70–100% absorbed in man and reach peak blood levels between 1–3 h after oral administration (Fitzgerald

& Scales, 1968; Paterson, Connolly, Dollery, Hayes & Cooper, 1970; Hicks, unpublished).

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REFERENCES

BECKETT, A. H. & TRIGGS, E. J. (1967). Buccal absorption of basic drugs and its application as an *in vivo* model of passive drug transfer through lipid membranes. *J. Pharm. Pharmac.*, **19**, 31S–41S.

DEARDEN, J. C. & TOMLINSON, E. (1971). A new buccal absorption model. *J. Pharm. Pharmac.*, **23**, 68S–72S.

FITZGERALD, J. D. & SCALES, B. (1968). Effect of a new adrenergic β-blocking agent (ICI 50,172) on heart rate in relation to its blood levels. *Int. Z. Klin. Pharmacol. Ther. Toxik.*, **1**, 467–474.

PATERSON, J. W., CONNOLLY, M. E., DOLLERY, C. T., HAYES, A. & COOPER, R. G. (1970). The pharmacodynamics and metabolism of propranolol in man. *Pharmacol. Clin.* **2**, 127–133.

Some behavioural and anticonvulsant actions in mice of ethanolamine O-sulphate, an inhibitor of 4-aminobutyrate aminotransferase

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Ethanolamine O-sulphate (EOS) is a specific active-site-directed irreversible inhibitor of 4-aminobutyrate aminotransferase (GABA-T) (Fowler & John, 1972a and b), the major catabolic enzyme for GABA in mammalian brain (Balazs, Machiyama, Hammond, Julian & Richter, 1970).

We have given EOS intracerebroventricularly to mice (method of Brittain & Handley, 1967), in order to re-investigate the possible relationship between elevated brain GABA concentrations and the response to maximum electroshock. Previous studies with non-specific inhibitors of GABA-T failed to establish a correlation (Kuriyama, Roberts & Rubenstein, 1966; Maynert, 1969).

Injection of 80–320 μg of EOS caused decreased locomotor activity, hunched posture, ptosis and hypothermia and these effects more closely resembled those of reserpine than of chlorpromazine. Such doses of EOS also protected against the hind limb extension induced by electroshock, the effect at 48 h being greater than at earler times. Whole brain concentrations of GABA were significantly increased 6 to 48 h after 160 μg EOS whereas 5-HT concentrations were only increased from 24 h.

The anticonvulsant studies revealed only weak protection against maximum electroshock during the first 36 h although GABA concentrations were greatly increased. The anticonvulsant activity of EOS over the first 36 h may be related to the increased 5-HT concentrations and it may be relevant that the action of anticonvulsant drugs has been associated with increased 5-HT concentrations (Bonnycastle, Giarman & Paasonen, 1957). However, the marked increase in anticonvulsant effect between 36 and 48 h was not paralleled by a corresponding elevation of brain 5-HT. The changes in 5-HT concentrations throughout the period of elevated GABA concentrations support the suggestion of Yessaian, Armenian & Buniatian (1969) that there may be an interrelationship between the GABA and 5-HT systems in brain.

REFERENCES

BALAZS, R., MACHIYAMA, Y., HAMMOND, B. J., JULIAN, T. & RICHTER, D. (1970). The operation of the γ-aminobutyrate bypath of the tri-carboxylic acid cycle in brain tissue *in vitro*. *Biochem. J.*, **116**, 445–467.

BONNYCASTLE, D. D., GIARMAN, N. J. & PAASONEN, J. K. (1957). Anticonvulsant compounds and 5-hydroxytryptamine in rat brain. *Br. J. Pharmac.*, **12**, 228–231.

BRITTAIN, R. T. & HANDLEY, S. L. (1967). Temperature changes produced by the injection of catecholamines and 5-hydroxytryptamine into the cerebral ventricles of the conscious mouse. *J. Physiol., Lond.*, **192**, 805–813.

FOWLER, L. J. & JOHN, R. A. (1972a). Active site directed irreversible inhibition of 4-aminobutyrate aminotransferase by ethanolamine O-sulphate. *Biochem. J.*, in press.

FOWLER, L. J. & JOHN, R. A. (1972b). Active site directed irreversible inhibition of rat brain 4-aminobutyrate aminotransferase by ethanolamine O-sulphate *in vitro* and *in vivo*. *Biochem. J.*, in press.

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

MAYNERT, E. W. (1969). The role of biochemical and neurohumoral factors in the laboratory evaluation of antiepileptic drugs. *Epilepsia*, **10**, 145–162.

YESSAIAN, N. H., ARMENIAN, A. R. & BUNIATIAN., H. Ch. (1969). Effect of γ-aminobutyric acid on brain serotonin and catecholamines. *J. Neurochem.*, **16**, 1425–1433.