Hypoxia and methionine sulphoximine seizures in mice

Acute exposure to hypoxia imparts protection against drug-induced convulsions (Baumel, Schatz & others, 1969a,b). If this is due to the elevated brain γ-aminobutyric acid observed in hypoxic animals (Wood, Watson & Ducker, 1968), drugs which cause convulsions by impairing γ-aminobutyric acid synthesis should become less toxic under hypoxia. Methionine sulphoximine inhibits synthesis of glutamine (Lamar & Sellinger, 1965), a precursor of brain γ-aminobutyric acid (Roberts & Frankel, 1951), and causes severe convulsions (Johnson, Goldring & O'Leary, 1965; Proler & Kellaway, 1962). We now report that acute hypobaric hypoxia antagonizes seizures produced by methionine sulphoximine.

Swiss albino, random-bred male mice (Charles River Farms), 30–35 g were housed at 21–23° with room lights alternating on a 12 h light-dark cycle. The hypobaric chambers (Baumel, Robinson & Blatt, 1967) were plexiglass desiccators (internal diameter 10 in, height 14 in) connected, in parallel, to a manifold which exhausted room air.

Drug solutions were freshly prepared immediately before intraperitoneal injection. The animals were injected and immediately placed, in pairs, in the 4 chambers which were then decompressed in 10 min to 364 mm Hg (10% O_2) or 12 min to 280 mm Hg (7·5% O_2).

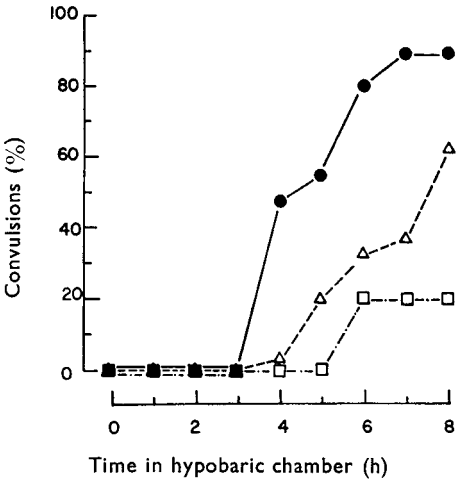

FIG. 1. Effect of hypobaric hypoxia on methionine sulphoximine (200 mg/kg intraperitoneally) convulsions. (—) Sea level, (- - -) hypobaric, ● 760 mm Hg, ▲ 364 mm Hg, ■ 280 mm Hg. Open symbols denote significant difference (P <0·005) from sea level.

Hypobaric hypoxia protected against methionine sulphoximine convulsions throughout the exposure period (Fig. 1). The anticonvulsant effect at 280 mm Hg was greater than at 364 mm Hg (8h convulsions, P <0·02). This resembles the dependence of brain γ-aminobutyric acid elevation under reduced oxygen tension on the degree of hypoxia employed (Wood & others, 1968).

Our data, along with previous findings with semicarbazide (Baumel, Schatz & others, 1969a, b), suggest that acute hypoxia prevents convulsions which are caused by the impairment of γ-aminobutyric acid synthesis.

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REFERENCES

BAUMEL, I. P., ROBINSON, S. M. & BLATT, W. F. (1967). *J. pharm. Sci.*, **56**, 918–919.
BAUMEL, I. P., SCHATZ, R., DEFEO, J. J. & LAL, H. (1969a). *J. Pharm. Pharmac.*, **21**, 119–120.
BAUMEL, I., SCHATZ, R., DEFEO, J. J. & LAL, H. (1969b). *Ibid.*, **21**, 475–476.
JOHNSON, W. L., GOLDRING, S. & O'LEARY, J. L. (1965). *Clin. Neurophysiol.*, **18**, 229–238.
LAMAR, C., JR. & SELLINGER, O. Z. (1965). *Biochem. Pharmac.*, **14**, 489–506.
PROLER, M. L. & KELLAWAY, P. (1962). *Epilepsia*, **3**, 117–130.
ROBERTS, E. & FRANKEL, S. (1951). *J. biol. Chem.*, **190**, 505–512.
WOOD, J. D., WATSON, W. J. & DUCKER, A. J. (1968). *J. Neurochem.*, **15**, 603–608.

The nature of the products from the reaction between Mayer's reagent and tertiary amines

Mayer's reagent (an aqueous solution of potassium tetra-iodomercurate) gives precipitates with alkaloids and synthetic tertiary amines. This reaction forms the basis of a qualitative test for such compounds. Szász (1965; 1966) has reported, from a study of seventeen tertiary amines, that each amine is capable of forming two compounds with potassium iodomercurate, the nature of the compound formed being dependent upon the concentration ratio of the reactants. An excess of potassium tetra-iodomercurate yields coloured (yellow or brown) products, whereas when the amine is in excess the resultant compound is white or only faintly coloured.

Because the "amine-Mayer's reagent" products are formed only in acidic medium, it is reasonable to assume that they are simple salts with a protonated amine cation and either a tri-iodomercurate or tetra-iodomercurate anion. Microanalytical data support the stoichiometry of this proposal (Szász & Buda, 1969). The reactions may, therefore, be expressed by the following equations:

$$(BH)^+ + (HgI_4)^{--} \rightarrow (BH)^+ (HgI_3)^- + I^-$$

and

$$2(BH)^+ + (HgI_4)^{--} \rightarrow (BH)_2^{++} (HgI_4)^{--}$$

To confirm the salt-like character of the "amine-Mayer's reagent" products, a proton magnetic resonance (pmr) investigation of two representative tertiary amines, codeine and *NN*-dimethylaniline and their iodomercurates was undertaken (Table 1).

The pmr spectrum of dimethylaniline in acetone-D_6 shows a normal $-N-(CH_3)_2$ singlet at 7·20 τ and a complex AA'BB'C aromatic pattern centred on 3·08 τ. This spectrum differs only marginally from that recorded in deuterochloroform (Ma & Warnoff, 1965; Anderson & Silverstein, 1965; Thompson, Warren & others, 1966). Protonation of the nitrogen, in the hydrochloride salt, results in the expected downfield shift of the *N*-methyl absorption to 6·59 τ and of the aromatic multiplet to 2·05 τ. The overall appearance of the aromatic multiplet is little changed. Dimethylaniline tri-iodomercurate and dimethylaniline tetra-iodomercurate exhibit their *N*-methyl signals at 6·36 and 6·42 τ respectively and both aromatic multiplets centre on 2·24 τ. Although these values correspond well with those of the simple hydrochloride and hydroiodide salts, the appearance of the aromatic multiplet is much changed in the iodomercurates.