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Investigations into the origin of the high pressure neurological syndrome: the interaction between pressure, strychnine and 1,2-propandiols in the mouse

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1 The effects of a variety of structural isomers of the centrally acting muscle relaxant mephenesin on the high pressure neurological syndrome have been investigated. Threshold pressures for the onset of the behavioural signs, tremors and convulsions, were established. The effects of these compounds on the response to pressure were also compared with their ability to antagonize the convulsive action of strychnine.

2 The dose-response relationships for strychnine and picrotoxin were investigated at fixed pressures. Additionally, the dose-response relationship of strychnine, in the presence of mephenesin, at pressure was investigated.

3 All the isomers of mephenesin protected against the effects of both pressure and strychnine. The relative potency was found to be identical with respect to both. Mephenesin was clearly the most effective; it raised the threshold pressure for tremors by 2.5 times, that for convulsions elicited by pressure by 1.5 and the ED_{50} for strychnine convulsions by 1.6 times. Strychnine was found to be strictly additive with pressure whereas picrotoxin exhibited gross deviations from additivity. Mephenesin ameliorated the combined effects of pressure and strychnine equally.

4 The marked dependence on structure of the anticonvulsant activity of the mephenesin isomers can be interpreted as evidence that pressure acts not by some general perturbation of the membranes of excitable cells but rather via some specific interaction. The finding that strychnine and pressure are strictly additive supports the idea of specificity and also indicates that they may share a common mechanism in the production of convulsions. By analogy with the established mechanism of action of strychnine, it is suggested that the hyperexcitability associated with pressure might arise from an action on glycine-mediated inhibitory processes.

Introduction

The stimulant action of pressure, described as the high pressure neurological syndrome (HPNS), has been observed in both man and animals and the manifestations are similar in both (Bennett, 1982; Brauer, 1975). In small rodents, at pressures above 20 bar tremors of the forelimbs are observed which progress to more pronounced movements of the hindlimbs. These become more severe with increasing pressure and faster rates of compression and at pressures above 70 bar develop into overt convulsions, culminating in death. At present divers work routinely at pressures up to 40 bar and experience the early stages of HPNS. With the increase in deep diving these effects constitute a potential hazard to the safety of divers.

The similarity between the effects of pressure on man and animals provides an opportunity to develop, in an animal model, pharmacological methods to protect divers from the adverse effects of high pressure. For example, the addition of an anaesthetic gas such as nitrogen to the oxy-helium breathing mixture (Trimix) has extended the pressure exposure of man to 70 bar (Bennett *et al.*, 1982). The use of Trimix arose from the well established interaction between pressure and general anaesthetics, first observed in animals, usually referred to as the

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pressure reversal of anaesthesia. This phenomenon has been interpreted by a physical model which describes the action of pressure in terms of changes in volume (Miller *et al.*, 1973). However, in this paper we seek to develop a more detailed understanding of the mechanisms by which pressure acts.

Neuroanatomical investigations have demonstrated that pressure has a sub-cortical site of action (Bowser-Riley *et al.*, 1981; Kaufmann *et al.*, 1981). Pharmacological experiments using a group of centrally acting propandiol muscle relaxants, whose actions are believed to be mediated sub-cortically (see Smith, 1965), have revealed some insights into the mechanism of action of pressure. The aromatic propandiols (related to mephenesin) confer substantial protection against HPNS whereas the aliphatic propandiols are ineffective (Bowser-Riley, 1984). This division of action reflects that observed with strychnine-, picrotoxin- and metrazol-induced seizures (Smith, 1965; Bowser-Riley, 1984); with the aromatic propandiols being effective against strychnine but not against picrotoxin or metrazol and with the reverse being the case with the aliphatic compounds. In addition it was found that strychnine potentiated the effects of pressure to a greater extent than did picrotoxin or metrazol. These findings, taken together, may suggest that pressure and strychnine share a common mechanism for the production of convulsions.

To test this assumption we have sought to evaluate the relationship between pressure and strychnine using two different approaches. First, we have used a series of structural isomers of the centrally acting muscle relaxant mephenesin, to test whether the relative potencies of anticonvulsant action exhibited against strychnine are the same as those observed for their action against pressure. Second, we have investigated the degree to which the effects of the convulsants strychnine and picrotoxin are additive with those of pressure, in order to assess the possibility of a common mechanism of action.

A preliminary communication of some of these results has been made to the Physiological Society (Bowser-Riley *et al.*, 1984) and to the Third International Conference on Molecular and Cellular Mechanisms of Anaesthesia (Smith *et al.*, 1986).

Methods

Male mice (CD1, Charles River) weighing between 22 and 25 g were used throughout. They were housed under standard conditions (21°C, 12 h light/dark cycle) and allowed free access to food and water.

Experiments at pressure utilized a 251 hyperbaric chamber (Anthony Pratt & Co. Ltd., Surrey; working pressure 400 bar) equipped with full environmental control (temperature, oxygen partial pressure, effluent gases etc.). Helium, in the presence of 1 bar oxygen, was used for all compressions, with a compression rate of 3 bar min^{-1}. Animals were compressed in groups of four and restrained within the chamber in a divided cylinder. Body temperature was monitored, in one mouse, via a rectal probe and was maintained between 36 and 37°C by adjusting the chamber temperature. Continuous video recordings of the animals behaviour were made during compression, which allowed subsequent analysis under conditions in which observer bias was controlled. The behavioural endpoints associated with HPNS were as previously defined and comprised; fine tremor, coarse tremor and convulsions (Bowser-Riley, 1984). Assessment of drug action was made from their ability to alter these endpoints. Drugs were injected intraperitoneally (i.p.) at the start of compression and the dose range was selected with reference to that previously established for mephenesin (Bowser-Riley, 1984). A randomised test sequence was employed and control values obtained throughout the course of the experiments.

An identical regime of drug/control treatments was used to assess the anticonvulsant action of the drugs against strychnine. Strychnine was administered i.p. and the number of mice convulsing in a 30 min period noted. A minimum of seven mice was used to determine each point on the dose-response curves and the ED_{50} for strychnine convulsions for each drug treatment was derived by Probit analysis (Finney, 1964).

For experiments in which the ED_{50} for strychnine or picrotoxin was established at fixed pressures of 1, 21, 41 and 61 bar a modified procedure was used. The convulsants were injected at pressure, though an in-dwelling subcutaneous (s.c.) cannula, using a remotely controlled injection apparatus (Bowser-Riley & Price, 1986). The cannula (Portex, 3FG) was inserted aseptically, under ether anaesthesia, at the base of the tail and adjusted so that the tip lay midway between the scapula. At least one hour was allowed for recovery to avoid any distortion of the results by residual anaesthetic. The animals were compressed at 3 bar min^{-1} (as above) with pauses in the compression at the relevant pressures. The convulsants were injected 5 bar below the holding pressure to allow time for absorption. As before, the observation period for the appearance of the first convulsion was 30 min. To investigate the anticonvulsant action of mephenesin against strychnine at fixed pressures of 1, 41 and 81 bar a similar experimental format was employed. For these experiments mephenesin was injected (s.c.) 5 min before strychnine via a second cannula which terminated over the sternum. In all cases the ED_{50} values for convulsions were derived as described above.

Table 1 High pressure neurological syndrome (HPNS) thresholds for CD1 mice treated (i.p.) with isomers of mephenesin

Drug	*Dose* (mmol kg^{-1})	*Number*	*Fine tremor*	*Coarse tremor*	*Convulsions*
Untreated		20	34 ± 2[a]	72 ± 1[a]	85 ± 2[a]
Vehicle		15	36 ± 1	73 ± 1	84 ± 1
Mephenesin	1.4	17	89 ± 3	117 ± 2	123 ± 2
m-Mephenesin	1.4	12	51 ± 2	73 ± 1[a]	98 ± 1
	1.9	12	68 ± 3	104 ± 2	118 ± 1
p-Mephenesin	1.4	12	48 ± 2	75 ± 3[a]	94 ± 3[b]
	1.9	12	55 ± 1	96 ± 1	114 ± 2
o-Chlorphenesin	1.4	12	45 ± 2	77 ± 2[a]	89 ± 2[a]
	1.9	12	83 ± 2	104 ± 1	115 ± 1
p-Chlorphenesin	1.4	12	61 ± 3	88 ± 2	103 ± 4
	1.9	12	93 ± 2	114 ± 2	129 ± 2
β-Naphthylesin	1.4	6	55 ± 3	86 ± 3	102 ± 3
	1.9	6	73 ± 2	94 ± 3	112 ± 4

Data represent mean pressures (in bar) ± s.e.mean.
[a] Not significant (by use of Student's *t* test) when compared to vehicle controls.
[b] Significantly different with $0.01 > P > 0.001$.
All other values significantly different with $P < 0.001$.

The compounds investigated were obtained from the following sources: (a) muscle relaxants: mephenesin (3[2-methylphenoxy]propan-1,2-diol; Sigma); *meta*-mephenesin (3[3-methylphenoxy]propan-1,2-diol), *para*-mephenesin (3[4-methylphenoxy]propan-1,2-diol), *para*-chlorphenesin (3[4-chlorphenoxy]propan-1,2-diol), *ortho*-chlorphenesin (3[2-chlorphenoxy]propan-1,2-diol) and napthylesin ([β-napthyloxy]propan-1,2-diol) were all kindly supplied by Dr E.W. Gill, University Department of Pharmacology, Oxford. (b) Convulsants: strychnine hydrochloride BP (Burroughs Wellcome), picrotoxin (Sigma).

All the compounds were administered in a volume of 0.1 ml at 37°C. The muscle relaxants were dissolved in a 10% ethanol saline and the convulsants in saline.

Results

All the muscle relaxants were effective in raising the pressure of onset for the behavioural endpoints associated with HPNS (see Table 1). The control thresholds and those obtained in the presence of 1.4 mmol kg^{-1} of mephenesin (*ortho* mephenesin) are close to those obtained previously (Bowser-Riley, 1984). The *meta* and *para* isomers of mephenesin at 1.4 mmol kg^{-1} did not raise the HPNS thresholds to the same degree as did mephenesin. In particular, there was no significant change in the threshold for coarse tremor. However, at the higher dose of 1.9 mmol kg^{-1}, the effects of the *meta* and *para* isomers also match those obtained with mephenesin. The order of potency for these compounds, for all the HPNS thresholds, was *ortho* > *meta* > *para*. The chloro-analogues of mephenesin, *ortho*-chlorphenesin and *para*-chlorphenesin, also raised the HPNS thresholds. In contrast to the mephenesin isomers, for these compounds the *para* isomer was more potent than the *ortho*, although neither compound was as potent as mephenesin. Similarly, the napthyl derivative of mephenesin (β-naphthylesin) raised all the thresholds for HPNS but was the least potent overall. Comparison of the untreated and vehicle-treated controls (Table 1) showed that the drug vehicle was without effect on the HPNS thresholds.

The changes in HPNS thresholds relative to control values for the most effective doses of the muscle relaxants are shown on Figure 1. This shows that their protective action is most marked on the early stages of HPNS. Mephenesin and *para*-chlorphenesin increased HPNS thresholds by a factor of 2.5 for fine tremor and 1.5 for coarse tremor and convulsions. All the remaining isomers, whilst less effective, showed a similar profile on the response to pressure.

The effects of mephenesin, *meta*- and *para*-mephenesin and *para*-chlorphenesin were tested on the convulsive action of strychnine (see Table 2). All the compounds increased the ED_{50} for strychnine convulsions and the increases in the ED_{50} relative to the control value, for the most effective doses of the compounds, are shown in Figure 1. The relative potency of these isomers of mephenesin is identical for protection against both pressure and strychnine, with a rank correlation coefficient (Kendall, 1955) of 1. It can be seen from Figure 1 that in all cases the

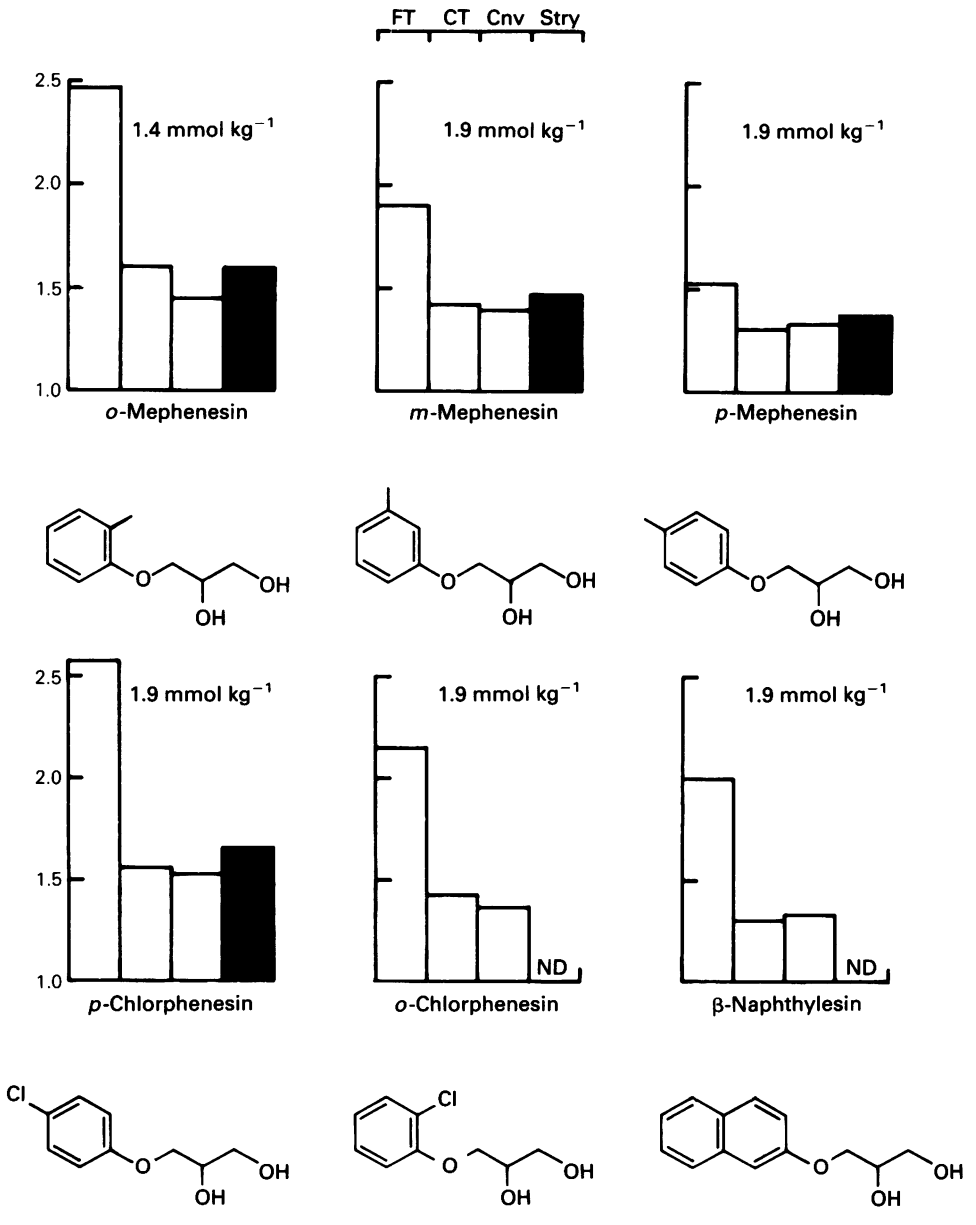

Figure 1 Relative changes in high pressure neurological syndrome (HPNS) thresholds for the actions on mephenesin isomers (i.p.) compared to control. Also shown are the relative changes in the ED_{50} for convulsions elicited by strychnine (i.p.) (denoted by solid columns). All the changes shown are significant ($P < 0.001$; Student's t test). Abbreviations used: FT, fine tremor; CT, coarse tremor; Cnv, convulsions; Stry, strychnine; ND, not determined.

relative increase in the convulsive thresholds is slightly greater for strychnine than for pressure.

The identical order of potency for these isomers of mephenesin for their anticonvulsive action against both strychnine and high pressure suggests that strychnine and pressure share a common mechanism of action. If this is the case, then it may be that the combined effects of strychnine and pressure would be simply additive. To test this possibility dose-response curves to strychnine (s.c.) were determined

Table 2 Anticonvulsant effects of isomers of mephenesin (i.p.) on convulsions elicited by strychnine (i.p.) in CD1 mice

Drug	*Dose* (mmol kg^{-1})	*Number*	*Strychnine* ED_{50} (μmol kg^{-1})
Control		42	3.15 ± 0.16
Mephenesin	1.4	30	5.04 ± 0.35
m-Mephenesin	1.4	24	4.07 ± 0.32[b]
	1.9	24	4.66 ± 0.32
p-Mephenesin	1.4	24	3.77 ± 0.18[a]
	1.9	36	4.15 ± 0.20
p-Chlorphenesin	1.4	24	4.28 ± 0.21
	1.9	30	5.31 ± 0.32

Results show mean values ± s.e.mean.
[a] Significant compared to controls (Student's *t* test) with $0.02 > P > 0.01$.
[b] Significant compared to controls with $0.01 > P > 0.001$.
All other values significant with $P < 0.001$.

at pressures of 1, 21, 41 and 61 bar. The semi-logarithmic plots of the dose-response curves (Figure 2) show a progressive shift to the left with increasing pressure. The ED_{50} values, derived by Probit analysis of the dose-response curves, for strychnine are shown in Table 3. The ED_{50}s for strychnine convulsions obtained at pressure, normalised relative to that obtained at 1 bar, are plotted (Figure 3) against the pressure at which they were obtained normalised relative to the ED_{50} for convulsions elicited by pressure alone (90 ± 0.6 bar; $n = 23$). The line (of unit slope) drawn between the normalised ED_{50} for strychnine and that for high pressure convulsions represents simple additivity. The experimental values fall close to the line with the deviation from linearity insignificant (correlation coefficient = 0.998; $P < 0.001$). This shows that the combined administration of the two agents in complimentary proportions of their ED_{50} values causes a similar effect as the ED_{50} for the action of either convulsive agent alone. Thus the combined action of pressure and strychnine are strictly additive and the two agents behave, from a pharmacological standpoint, as though they were identical.

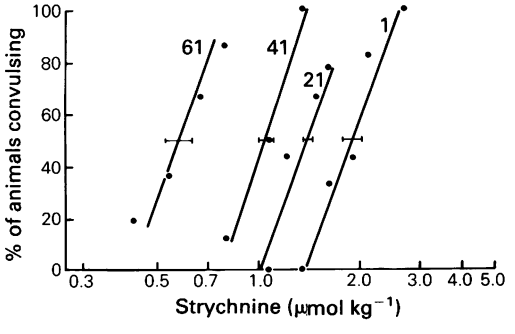

Figure 2 Semi-logarithmic dose-response curves for strychnine (s.c.) established at pressures of 1, 21, 41 and 61 bar. The s.e. of the ED_{50}, determined by probit analysis, is shown in each case (denoted by horizontal bars).

The dose-response relationship for convulsions elicited by picrotoxin was also investigated at pressures of 1, 41 and 61 bar. The ED_{50}s derived from the dose-response data are given in Table 3. There was no significant difference between the values obtained at 1 and 41 bar, although the value obtained at 61 bar was significantly reduced. These results were evaluated in the same way as for strychnine and are illustrated in Figure 3. In contrast to the interaction between pressure and strychnine the experimental values obtained for picrotoxin significantly deviate from linearity. It is clear from these results that the interaction between pressure and picrotoxin is grossly non-additive.

To determine, more directly, whether the anticonvulsive effects of mephenesin against pressure and strychnine share a similar mechanism the interaction between strychnine, pressure and mephenesin was investigated. The results of these experiments, in which the ED_{50} for strychnine convulsions was established at pressures of 1, 41 and 81 bar following the subcutaneous administration of 0.7 mmol kg^{-1} of mephenesin, are given in Table 4. At 1 bar, mephenesin increased the ED_{50} for strychnine from 1.85 μmol kg^{-1} to 3.39 μmol kg^{-1}. This value was progressively reduced at higher pressures. When these results were normalised as previously, then the relationship illustrated in Figure 3 was obtained. It can be seen that the effects of both strychnine and pressure are ameliorated to the same degree by mephenesin, so that combined effects of the agents remained additive but that higher doses were

Table 3 ED_{50} values (μmol kg^{-1}) for strychnine and picrotoxin convulsions at pressure

Pressure (bar)	*PN*	*Strychnine* (mean ± s.e.mean)	*SN*	*Number*	*Picrotoxin* (mean ± s.e.mean)	*PcN*	*Number*
1	0.01	1.85 ± 0.08	1.00	42	2.90 ± 0.20	1.00	76
21	0.23	1.37 ± 0.05	0.74	34			
41	0.45	1.02 ± 0.02	0.55	26	3.20 ± 0.27[a]	1.10	54
61	0.68	0.57 ± 0.05	0.30	34	2.06 ± 0.17[b]	0.71	32

PN gives the pressure normalised relative to the ED_{50} pressure threshold for convulsions (90 ± 0.6 bar; $n = 23$). SN and PcN give the ED_{50}s at pressure for strychnine and picrotoxin respectively normalised relative to that for strychnine and picrotoxin alone.

[a] Not significant compared to value at 1 bar (Student's t test).

[b] Significant compared to value at 1 bar with $0.02 > P > 0.01$.

All other values significant with $P < 0.001$.

required in the presence of mephenesin to restore the original level of the response.

Discussion

The various phenoxy-1,2-propandiols used in this study showed a remarkable ability to protect against HPNS. The most effective compounds, mephenesin and *para*-chlorphenesin, have been shown to increase the pressure threshold for fine tremor by a factor of 2.5 and those for coarse tremor and convulsions by 1.5. This degree of protection is comparable to that previously obtained for the most effective non-anaesthetic anti-HPNS drug 2-amino-7-phosphoheptanoic acid (APH) which increased the tremor threshold by a factor of 2.3 and that for convulsions by 1.25 (Meldrum *et al.*, 1983). This marked protection against the early stages of HPNS is a characteristic feature of the anti-HPNS properties of both the aromatic propandiols and APH as well as other, less effective, anti-HPNS drugs such as sodium valproate and flurazepam (Bowser-Riley, 1984). It has been suggested that this differential action arises because the different phases of HPNS have different sites of origin (Meldrum *et al.*, 1983). Alternatively, since the relative changes in potency against the various phases of HPNS of all the propandiols used in this study showed a common pattern (see Figure 1), the different components of HPNS may well be manifestations of a single response to pressure and represent a progression of effects which culminate in convulsions.

Table 4 ED_{50} values (μmol kg^{-1}) for strychnine (s.c.) convulsions in the presence of mephenesin (0.7 mmol kg^{-1} s.c.) at pressures of 1, 41 and 81 bar

Pressure (bar)	*PN*	*ED_{50}*	*SmN*	*Number*
1	0.01	3.39 ± 0.13	1.83	26
41	0.45	2.42 ± 0.08	1.31	33
81	0.90	1.42 ± 0.08	0.77	23

SmN gives the ED_{50} normalised relative to that for strychnine alone. PN gives the pressure normalised relative to the ED_{50} pressure threshold for convulsions (90 ± 0.6 bar; $n = 23$).

The ED_{50}s shown represent means ± s.e.mean.

The properties of the mephenesin isomers were investigated by Berger (1952), who found that the anticonvulsant potency against strychnine depended on both the position and the nature of the substituent group on the aromatic ring. We have found that, similarly, there is an ordered potency of the isomers against convulsions elicited by pressure. The marked differences in potency of these simple isomers suggests that pressure may exert its action not by a general perturbation of the bulk properties of the lipid portion of the cell membrane, as has been widely believed (Miller, 1985), but rather by some more specific action. The results of the present work which show an identical potency of the mephenesin isomers against both strychnine and pressure, suggest tht the mechanisms of action of pressure may be linked to that of strychnine.

Although the findings support the notion that pressure may exert its action via some effect at a strychnine-sensitive site, it would be rash to assume that the action of pressure was mediated exclusively in this way. Indeed, a role for cortical modulation of HPNS involving the monoaminergic neurotransmitters has been proposed (Brauer, 1975; Bowser-Riley, 1984) and alternative models to account for the subcortical convulsive action of pressure have been presented. Agents that potentiate the action of γ-aminobutyric acid (GABA) increase the thresholds for HPNS and this protection correlated with their ability to antagonize the seizures induced by the GABA antagonist bicuculline (Bichard & Little, 1982). However, the discovery that muscimol, a $GABA_A$-receptor agonist (Bichard & Little, 1984),

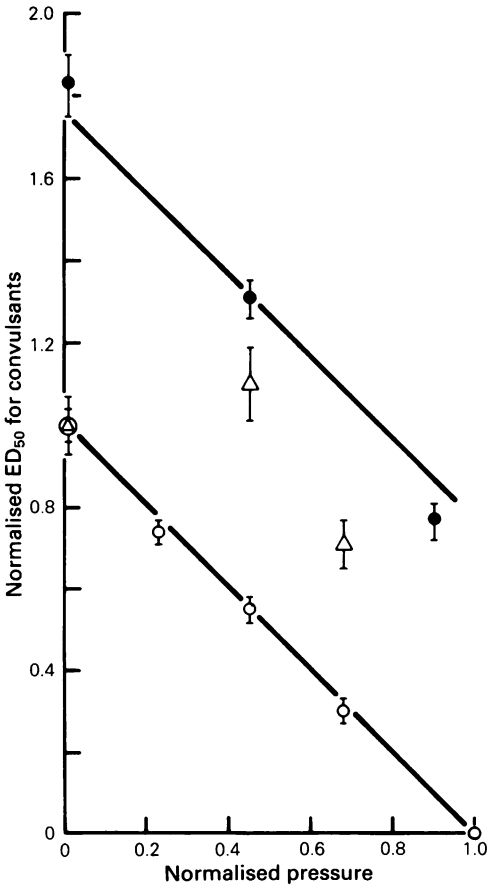

Figure 3 ED_{50} values for strychnine (○) and picrotoxin (△) normalised relative to their ED_{50}s at 1 bar plotted against the pressure at which they were determined normalised relative to the ED_{50} for convulsions elicited by pressure alone. The line of unit slope drawn between the normalised ED_{50} for strychnine at 1 bar and that for pressure alone represents simple additivity. The correlation coefficient for the fit of the strychnine ED_{50}s to the line showing simple additivity is 0.998 ($P < 0.001$), that for the picrotoxin ED_{50}s is 0.727 (not significant). The ED_{50}s for strychnine at pressure in the presence of mephenesin (0.7 mmol kg^{-1}, s.c.) are shown by (●). The upper line is drawn parallel to that showing simple additivity. In this case the correlation coefficient for the strychnine ED_{50}s is 0.999 ($0.05 > P > 0.02$).

and baclofen, a $GABA_B$ receptor agonist (Bowser-Riley, 1984), are ineffective against HPNS and that the convulsive action of picrotoxin is not additive with that of pressure, all suggest that GABA may not play a direct role in determining the response to pressure. The suggestion that pressure may bring about its effects by an intensification of excitatory mechanisms linked to the dicarboxylic acid transmitters, aspartate and glutamate, was proposed to explain the anti-HPNS actions of APH and PDA (*cis*-2,3-piperidine dicarboxylic acid) (Meldrum *et al.*, 1983; Wardley-Smith & Meldrum, 1984). Nevertheless, there is at present no evidence to show that either glutamate or aspartate mediate the primary effect of pressure.

The strict additivity observed between the convulsive actions of pressure and strychnine provides powerful evidence for a common mechanism of action. That the additive interaction between pressure and strychnine is not a feature common to a combination of pressure and any analeptic was demonstrated by the experiments with picrotoxin, where gross deviations from linearity were observed. The fact that even in the presence of mephenesin, strychnine and pressure remained strictly additive, provides further support for the suggestion that they share a common mechanism. The congruent behaviour of mephenesin with pressure and strychnine is of particular interest since there is, at present, no evidence to link directly the anticonvulsant properties of mephenesin with strychnine-related mechanisms. However, the present work suggests that the possibility of such an interaction cannot be discounted. Since it is widely held that strychnine exerts its convulsive action by depressing the postsynaptic inhibition mediated by glycine (e.g. Eccles, 1964; Curtis & Johnson, 1974), it is not unreasonable to assume that a major component of the action of pressure arises via the same mechanism.

The identification of a specific mechanism for the action of pressure on the central nervous system may provide an opportunity for the more rational development of improved strategies to protect divers against the adverse effects of high pressure.

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