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DRUGS THAT INCREASE γ-AMINOBUTYRIC ACID TRANSMISSION PROTECT AGAINST THE HIGH PRESSURE NEUROLOGICAL SYNDROME

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1 The effects on the high pressure neurological syndrome (HPNS) of drugs which facilitate γ-aminobutyric acid (GABA) transmission were investigated. Threshold pressures for the onset of the behavioural signs of the HPNS in mice – tremors and convulsions were established.

2 Flurazepam hydrochloride 20 and 10 mg/kg and sodium valproate 800 and 400 mg/kg substantially raised the threshold pressures for both tremor and convulsions.

3 Amino-oxyacetic acid 35 and 25 mg/kg and diaminobutyric acid 600 mg/kg also significantly increased the thresholds. Muscimol 1 mg/kg (and 150 ng i.c.v.) was ineffective at non-toxic doses.

4 These effects paralleled the drugs' ability to raise the convulsion threshold to intravenous infusion of bicuculline in mice.

5 These results demonstrate that drugs with actions more selective than those of the general anaesthetics are effective against the HPNS. It is also possible that there is a GABAergic component to the effects of general anaesthetics on the HPNS.

Introduction

The high pressure neurological syndrome (HPNS) is the state of hyperexcitability produced *in vivo* when the ambient pressure is increased using helium gas or hydrostatic pressure. The HPNS, now described in many species, is characterized in mammals by tremors, beginning at 30–50 atmospheres, followed by convulsions at approximately 70–100 atmospheres. Death occurs at around 100–130 atmospheres. The initial stages have been experienced by man during deep sea diving. Little is known about the physiological changes underlying the syndrome. EEG recordings made at the onset of convulsions have not indicated a definite focal site of origin, paroxysmal spike and wave patterns being recorded from many brain areas and in spinal cord (Kaufmann, Bennett & Farmer, 1977; 1981), although there is some evidence to suggest a subcortical origin (Brauer, 1975).

Until recently, the only pharmacological agents known to be effective against this syndrome were the general anaesthetics. These postpone the appearance of the signs to higher pressures, although the correlation between this action and their general anaesthetic potency is not good (Green, Halsey & Wardley-Smith, 1977). A reciprocal antagonism is seen, as pressure reverses the effects of general anaesthetics (Lever, Miller, Paton & Smith, 1971.) These interactions are seen with all types of general anaesthetics, including the barbiturates and steroids.

Clinically used anticonvulsants, such as ethosuximide or carbamazepine, do not raise the threshold pressure for onset of convulsions (Halsey & Wardley-Smith, 1980) although phenobarbitone is effective, more so than pentobarbitone (Beaver, Brauer & Lahser, 1977).

In the pattern of drug susceptibility therefore, the HPNS convulsions do not resemble closely any other types of convulsions. Certain similarities have been described, however, to pentylenetetrazol (Ptz) convulsions with regard to species and ontogenic variation (Brauer, Beaver, Lahser, McCall & Venters, 1979) and to Ptz, electroshock and auditory convulsions in the potentiation caused by lowered central monoamine concentrations (Brauer, Beaver & Sheehan, 1978; Koblin, Little, Green, Daniels, Smith & Paton, 1980).

The use of agents effective against the HPNS in deep sea diving is at present limited to the addition of nitrogen to helium/oxygen breathing mixtures. Drugs which oppose the HPNS without causing general anaesthesia have potentially useful practical applications and may also provide clues as to the changes underlying the syndrome and the effects of general anaesthetics.

The involvement of γ-aminobutyric acid (GABA) in experimental convulsions is well known. Decreases in central GABA function are associated with the occurrence of convulsions and drugs which potentiate GABA transmission are effective in preventing many types of convulsions. The present study was designed to examine the effects on the convul-

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sions of high pressure of drugs which potentiate GABA-mediated transmission.

Although such potentiation is possible by various pharmacological means, the drugs available are not completely specific. It was hoped that by the use of several drugs with different mechanisms of action the involvement of GABA might be clarified. The drugs used were amino-oxyacetic acid (AOAA) which inhibits GABA-transaminase; 2,4-diaminobutyric acid (DABA) which blocks the reuptake of GABA; sodium valproate which inhibits succinic semialdehyde dehydrogenase and may also have additional postsynaptic actions (Kerwin, Olpe & Schmutz, 1980); muscimol which is an agonist at the GABA receptor and flurazepam, a benzodiazepine that potentiates transmission by action at the GABA-receptor complex.

In order to compare the effectiveness of these drugs against convulsions which were known to be due to decreased GABA function, their ability to prevent convulsions produced by intravenous infusion of bicuculline was also assessed.

Methods

High pressure experiments

Male CDI mice were injected intraperitoneally (i.p.) with coded solutions before being placed, individually, in a 1.9 litre pressure chamber. The pretreatment times between drug administration and start of compression are given in Table 1. A rectal probe was inserted (2 cm deep) in each animal and taped to the tail. Body temperature was monitored throughout every experiment on a chart recorder.

At the beginning of each experiment, before compression, the chamber was flushed for 4 min with 100% oxygen. The oxygen partial pressure was therefore close to 1 atm initially. Helium gas was added continuously at the rate of 3 atm per min. The chamber atmosphere was continuously mixed by an induction motor fan and both soda lime and activated charcoal were present to absorb carbon dioxide and any effluent gases.

The animals were observed using a closed circuit video system, with a televison camera sighted through a porthole in the chamber and an external lighting system. Tremors were defined as continuous shaking of whole body and limbs. The pressures were noted for the onset of convulsions, defined as a clonic seizure severe enough to prevent the animal righting itself. Clonic seizures were occasionally interrupted by periods during which the animal adopted a rigid posture, but true tonic seizures with full limb extension were not seen. All observations were rated blind and coded solutions were used for all injections. A random order of treatments (including controls) was used so that control values were established throughout the course of experiments.

The drugs were injected by the intraperitoneal route. Sodium valproate and flurazepam were given immediately prior to pressurization, while AOAA, DABA and muscimol were given 1 h before. (For AOAA this time of pretreatment does not correlate with its maximum effect on central GABA concentrations but is the time at which clear anticonvulsant actions have been demonstrated, which may reflect the lack of correlation of total GABA concentrations with synaptic changes; Wood & Peesker, 1975).

The body temperature was maintained at 37°C ± 1.5°C throughout the experiments by alterations in internal chamber temperature using circulating water heat exchangers outside the chamber. In the majority of experiments temperature control to ± 1°C was possible.

In some experiments muscimol was injected into the cerebral ventricles. The effectiveness of this method was checked by administration of dye (Pontamine Sky Blue). Following such injections the dye was found to be restricted to the third and lateral ventricles. The maximum volume used for injection was 0.25 ml i.p. and 1 μl i.c.v.

Bicuculline infusion studies

The anticonvulsant actions of the drug treatments were established using an intravenous infusion of bicuculline, according to the method of Nutt, Cowen & Green (1980). This involved the infusion of bicuculline (at 1.5 ml/min, concentration 50 μg/ml) into the tail vein of mice until a full convulsion occurred. The dose of bicuculline (mg/kg) calculated from the time to convulsions was used as an index of the threshold. Control threshold values (after saline injection) were established for each experiment.

Preliminary experiments using bicuculline were carried out with all the drugs in order to determine the effective doses and pretreatment times. When their effects on the pressure thresholds had been established a detailed study was made of their effects against bicuculline. In this part of the work the anticonvulsants were given so that the time between treatment and the start of bicuculline infusion was the same as that between administration of the drugs and the observed occurrence of the convulsions under pressure. The temperature of the mice was monitored throughout this part of the work and maintained at 37°C ± 1°C.

Statistical analysis

The significance of the results was determined using the Mann-Whitney 'U' test. Spearman rank correla-

Table 1 Effects of drug treatments on onset pressures for tremor and for convulsions

Drug	*Dose* (mg/kg)	*High pressure thresholds* *Tremor* (atm)	*Convulsions*	n
Group 1				
Control	–	63 ± 3	79 ± 2	(6)
Sodium valproate	400	82 ± 1*	125 ± 1*	(6)
Sodium valproate	800	110 ± 4*	133 ± 4*	(6)
Flurazepam	10	91 ± 2*	113 ± 3*	(6)
Flurazepam	20	95 ± 2*	111 ± 2*	(6)
Group 2				
Control	–	65 ± 1	82 ± 1	(6)
AOAA	25	76 ± 1*	94 ± 2*	(6)
AOAA	35	80 ± 4*	100 ± 2*	(6)
DABA	600	78 ± 3*	95 ± 3*	(6)
Muscimol	1	70 ± 2	85 ± 2	(6)

Values are given ± s.e.mean. AOAA amino-oxyacetic acid; DABA 2,4-diaminobutyric acid. Injections were made immediately before (Group 1) or 1 h before (Group 2) start of pressurization. n = number of mice; * $P < 0.001$ (Mann-Whitney 'U' test).

tion coefficients were calculated (Siegel, 1956) for the percentage changes in convulsion thresholds with bicuculline and with pressure and for the changes in pressure thresholds to tremors and to convulsions.

Results are presented as means ± standard error of the mean (s.e.mean).

Drugs

The following drugs were used: amino-oxyacetic acid (Sigma); (+)-bicuculline (Sigma); L-2,4-diaminobutyric acid (Sigma); flurazepam (gift of Roche Ltd); muscimol (Sigma); sodium valproate (sodium n-dipropylacetate) (gift of Reckitt and Colman Ltd). All drugs except bicuculline were dissolved in sterile, isotonic saline immediately before use. Bicuculline was dissolved in 0.1 N HCl, titrated to pH 3.0 with 1 N NaOH then diluted with pH 3.0 isotonic saline to the required concentration.

Results

Sodium valproate (800, 400 mg/kg) and flurazepam hydrochloride (20, 10 mg/kg) were highly effective ($P < 0.001$) in raising the threshold pressure for onset of both tremors and convulsions (Table 1). Threshold pressures were increased relative to saline controls by between 30–75% for tremor and 40–60% for convulsions. AOAA (35, 25 mg/kg) and DABA (600 mg/kg) were also effective, with percentage increases of 17–27% for tremor and 15–22% for convulsions.

The effects of the drugs on seizure threshold to bicuculline are given in Table 2. The changes were broadly similar to those found in the pressure experiments, with two main differences. Firstly, the effects on bicuculline thresholds were greater, in terms of percentage changes. Secondly, the effects of the higher doses of Na valproate and flurazepam were greater than those of the lower doses, whereas there was little difference between their effects on the pressure thresholds. In order to determine how far the effects of the drugs on the HPNS paralleled their effects on

Table 2 Effects of drug treatments on bicuculline thresholds

Drug	*Dose* (mg/kg)	*Convulsion thresholds* (mg/kg)	n
Group 1			
Control	–	0.92 ± 0.03	(6)
Sodium valproate	400	1.82 ± 0.13*	(8)
Sodium valproate	800	2.80 ± 0.13*	(6)
Control	–	0.93 ± 0.04	(7)
Flurazepam	10	1.68 ± 0.07*	(6)
Flurazepam	20	2.10 ± 0.11*	(6)
Group 2			
Control	–	0.84 ± 0.04	(5)
AOAA	25	1.37 ± 0.04*	(6)
AOAA	35	1.50 ± 0.06*	(5)
Control	–	0.95 ± 0.03	(6)
DABA	600	1.39 ± 0.04*	(6)
Muscimol	1	1.29 ± 0.04*	(6)

Values are given ± s.e.mean. AOAA amino-oxyacetic acid; DABA 2,4-diaminobutyric acid. Injections were made immediately before (Group 1) or 1 h before (Group 2) start of pressurization. n = number of mice; * $P < 0.001$.

bicuculline convulsions, the percentage increases in threshold for convulsions caused by the HPNS and by bicuculline were compared (Figure 1). The Spearman rank correlation coefficient was 0.91 ($P < 0.05$). However, it is clear from this figure that the relationship between the effects on the two types of convulsions is not truly linear as the effects of sodium valproate and of flurazepam on the HPNS appear to have reached a peak.

Muscimol (1 ml/kg) did not cause any significant change in either tremor or convulsion thresholds and was also the least effective treatment against bicuculline. The effects of intracerebral injection of muscimol were also tested, as it has been reported to cross the blood-brain-barrier poorly; these results are not included in the tables as the compression rate used was slightly lower (1 atm/min) but no significant effects on thresholds were seen. The dose of muscimol used was limited by the occurrence of convulsions at doses of 2 mg/kg i.p. or 600 ng i.c.v. Excitant effects of muscimol have been described previously (Pedley, Horton & Meldrum, 1979) and these are thought not to be due to its GABA agonist activity (Menon & Vivonia, 1981a, b). Convulsant actions have also been reported with high doses of AOAA and DABA.

There was a significant correlation between the drugs' effects on the high pressure tremor and high pressure convulsion thresholds. r_s for the percentage changes is 0.91, $P < 0.01$. This pattern is in contrast

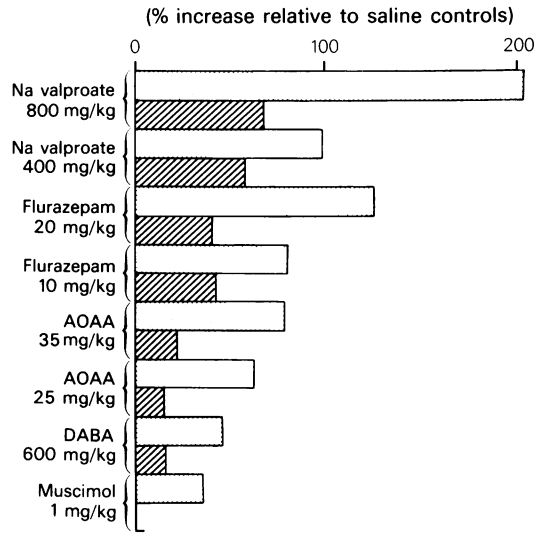

Figure 1 Comparison of changes in convulsion thresholds after bicuculline infusion (stippled column) and after application of high pressure (hatched column). Column lengths represent the percentage increases in thresholds relative to saline control values. AOAA amino-oxyacetic acid; DABA 2,4-diaminobutyric acid.

to the effects of other anticonvulsant drugs (see Discussion). The drugs used did not have any overt effects on the behaviour of the animals, with the exception of the 800 mg/kg dose of valproate and the muscimol. These caused muscle relaxation and slight ataxia. Righting reflex was clearly maintained after all treatments. The effects of the drugs on temperature were monitored in separate experiments and the higher dose of sodium valproate, the higher dose of flurazepam, the DABA and the muscimol dose all lowered body temperature by over 1°C in uncontrolled conditions. However, as body temperature was maintained in both pressure and infusion experiments and as muscimol had no significant effect on pressure thresholds, it is unlikely that the protection seen against the HPNS was connected with the hypothermic actions of the drugs.

Discussion

These results show that four drugs which increase GABA function in different ways significantly postponed the behavioural effects of helium to higher pressures. This protection was observed at doses of the drugs that had no overt effects on behaviour. The effectiveness of the benzodiazepines has been shown previously (Gran, Coggin & Bennett, 1980; Halsey & Wardley-Smith, 1981), but studies in this laboratory (Jackson, 1978) showed that the vehicle in which these drugs are dissolved (based on propylene glycol) had anti-HPNS action of its own. The present results with the water soluble flurazepam show that the benzodiazepine structure is effective, at doses as low as one twentieth of those which affect the righting reflex (the ED_{50} for loss of righting reflex was measured and found to be 280 mg/kg, with 95% confidence limits of 262–300 mg/kg).

The initial oxygen pressure in the chamber experiments was close to one atmosphere. There have been several suggestions that the convulsions produced by oxygen (at 3–6 atm) are caused by changes in GABA metabolism (Paton, 1967; Wood, Watson & Ducker, 1967). This raises the possibility that the effects of the drugs seen in our experiments may have been due to removal of the effects of subthreshold concentrations of oxygen. However, this is very unlikely as it has been demonstrated that neither amino-oxyacetic acid nor sodium valproate have any protective effect against oxygen convulsions (Wood & Watson, 1965; Brue, Joanny, Chaumont, Corriol & Broussolle, 1981) and Brauer, Way, Jordan & Parrish (1971) have shown that changes in oxygen partial pressure between 0.4 and 2 atm did not alter HPNS convulsion thresholds.

We conclude from the results that the increases in tremor and convulsion thresholds seen with sodium

valproate, flurazepam, DABA and AOAA were due to facilitation of GABA transmission by these drugs. Evidence for this is firstly that four drugs which facilitate GABA by different mechanisms were effective and secondly that their effectiveness against the HPNS was very similar to that against bicuculline convulsions. There were two aspects in which the effects of the drugs on the pressure thresholds differed from their effects on bicuculline convulsions. The extent of the changes in pressure thresholds produced by the drugs was less than that of the changes in bicuculline thresholds, when expressed in terms of percentage changes. (The lack of effect of muscimol at pressure in fact follows the pattern seen with the other drugs as it was the least effective against bicuculline.) In addition, there appeared to be a limit to the extent to which sodium valproate and flurazepam were able to postpone the pressure signs as the higher doses did not cause much greater changes than the lower ones, in contrast to their effects on bicuculline thresholds. This suggests that there may be a limit to the extent to which facilitation of GABA transmission can postpone the HPNS to higher pressures.

Previously the only drugs without general anaesthetic activity that had actions on the HPNS were two steroid isomers which provided partial protection against tremors (Wardley-Smith & Halsey, 1981), and phenytoin which decreased tonic/clonic convulsions but potentiated the other signs (Brauer *et al.*, 1979). The anticonvulsants which have been demonstrated to be ineffective against the HPNS are those for which GABA is not implicated as the primary mechanism of action; for example, ethosuximide, carbamazepine (Halsey & Wardley-Smith, 1981).

The effects of general anaesthetics on the HPNS have been attributed to their nonspecific actions on membrane properties (Lever *et al.*, 1971). The results described here may also be of relevance to the variation in the effectiveness of general anaesthetics against the HPNS (see Introduction). Some, but not all, general anaesthetics have actions that facilitate GABA transmission (for example, Nicoll, 1977; Huang & Barker, 1980), and this may contribute to their anti-HPNS actions, in addition to their nonspecific effects. It is possible that the drugs used in the present experiments had nonspecific actions, especially at the higher doses, but the lack of dose-dependence in the effects of flurazepam and of valproate at pressure suggests that this was not the basis of the changes seen.

Changes in GABA transmission may be involved in the genesis of the HPNS and in this connection it is of interest that the effects of these drugs on tremor and on convulsion thresholds at pressure were similar ($r_s = 0.91$) suggesting the possibility of a common mechanism. Little information is available about the actions of pressure on synaptic transmission but work in this laboratory is in progress to determine the effects on GABA transmission *in vitro* (Little, 1981). One report has been made of increased central GABA concentrations after pressurization (Ritter, Vandrovec & Wilson, 1969) but the analysis was carried out after 24 h at pressure (20–60 atm) followed by a graded decompression so that interpretation of the results is complicated by the possibilities of change during decompression and adaptive changes at pressure.

In addition to their possible theoretical importance the discovery of drugs effective against the HPNS that have actions more specific than those of the general anaesthetics may have a practical application in deep sea diving.

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