Mechanistic Studies on the High Pressure Neurological Syndrome [and Discussion]

F. Bowser-Riley, H. J. Little and R. W. Brauer

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Mechanistic studies on the high pressure neurological syndrome

By F. Bowser-Riley

University Laboratory of Pharmacology, South Parks Road, Oxford, OX1 3QT, U.K.

The high pressure neurological syndrome (h.p.n.s.) constitutes a major barrier to deep sea exploration by man. Although the signs and symptoms of h.p.n.s. are well documented in both man and experimental animals, the underlying mechanisms remain to be elucidated. Physiological and pharmacological evidence will be presented that confirms that the principal sites of action of pressure are within the central nervous system (c.n.s.). Results from physiological studies not only indicate that there are separate sites of action of pressure within the c.n.s., which mediate the different components of h.p.n.s., but also the response to pressure may be controlled by descending inhibitory pathways. Pharmacological studies support this view and suggest that h.p.n.s. involves a failure of central inhibition.

Introduction

The invariable consequence of the progressive application of high pressure is the appearance of a convulsive state, which has been described as the high pressure neurological syndrome (h.p.n.s.). In animals the stimulant action of pressure is manifested not only as convulsions but also by the earlier appearance of pronounced tremors and a variety of stereotyped movements (Brauer 1975), which may be classified as preconvulsive hyperexcitability. In man, although overt convulsions have not been reported, the preconvulsive hyperexcitability includes tremors of the hands and arms, involuntary leg movements, and e.e.g. abnormalities (Bennett 1975). For both man and animals symptoms become more severe with both increasing pressure and faster rates of compression. While the effects of pressure have been well characterized, the underlying mechanisms remain obscure.

The action of pressure might be regarded as analogous to other forms of hyperexcitability such as epilepsy. However, animal experiments have shown that high pressure convulsions are remarkably resistant to treatment with classical anti-epileptic agents (Halsey & Wardley-Smith 1981). It is worth stressing, therefore, that the effects of pressure, in common with other induced seizures, may result when normal neurons or neuronal systems are made to discharge in an abnormal fashion, in a manner quite different from the discharge of abnormal neurons at an epileptic focus.

With this in mind, we have sought a deeper analysis of the actions of pressure; first, to establish the site of initiation of the convulsive event and secondly, to investigate the actions of a variety of centrally acting agents at pressure, so as to define to some extent what type of convulsive activity pressure elicits.

Experimental procedure

We have employed a relatively straightforward method to assess the effect on h.p.n.s. of a variety of procedures. This consisted of the pressurization with helium (3 atm min^{-1}; O$_2$

pressure, 1 atm†) of CD-1 mice (20–25 g) in a pressure vessel equipped with a CO_2 scrubber, temperature sensors and internal heating control. Animal temperature was maintained between 36 °C and 37 °C. Continuous video recordings of animal behaviour were made during compression, which allowed subsequent playback for analysis under conditions in which observer bias was controlled. Assessment of the effect of a procedure was made from its ability to alter the following behavioural end points associated with h.p.n.s: (a) fine tremor, trembling of the head, neck and forelimbs; (b) coarse tremor, pronounced shivering of the whole body together with involuntary movement of the hind limbs; (c) convulsions, a sequence of uncoordinated, violent involuntary movements of sufficient severity to cause total loss of balance; (d) death, cessation of respiratory or other distinguishable movement, or both, for a period greater than 1 min.

NEUROANATOMICAL STUDIES

Previous suggestions that high pressure convulsions are initiated sub-cortically arose from electrophysiological experiments in which mass discharges from sub-cortical structures were found to precede those observed in the cortex (Brauer et al. 1979). In addition, the finding that immature mice were susceptible to the actions of pressure was taken to indicate that a functional cortex was not essential for the expression of high pressure convulsions (Mansfield et al. 1974). Therefore, to establish the site of action for pressure, experiments were made with classical ablation methods employing chronically prepared decerebrate and decorticate animals. Decerebrations were made by transection of the neuroaxis at the level of the colliculi. The decortication was performed by employing careful dissection and finely controlled suction to maintain, as far as possible, the integrity of the sub-cortical structures. With both techniques a minimum period of 24 h was allowed for post-operative recovery, to avoid distortion by any residue of the anaesthetic used during the operative procedures.

TABLE 1. H.P.N.S. THRESHOLDS ($\pm$s.e.)/ATM OF NORMAL, DECORTICATE
AND DECEREBRATE CD-1 MICE

	fine tremor	coarse tremor	convulsions	n
controls	46 ± 2	71 ± 4	100 ± 5	8
decorticate	$30 \pm 2^{(a)}$	$67 \pm 2^{(b)}$	$76 \pm 3^{(c)}$	5
decerebrate	nil	nil	$68 \pm 1^{(d)}$	6

(a) Probability, $p < 0.001$ against control; (b) $p \approx 0.6$ against control; (c) $p < 0.01$ against control; (d) $p < 0.001$ against control; $p < 0.05$ against decorticate.
Compression rate = 1 atm/min

Table 1 shows the threshold pressures at which fine tremors, coarse tremors and convulsions occur in these animals. The lethal pressure was not determined, since it was usual to recover the animals alive by slow decompression for assessment of the extent of the lesions, undistorted by bubble formation. Compared with controls, decortication significantly reduced the fine tremor threshold, had little effect on coarse tremors, and reduced the convulsive threshold by about 24%. In decerebrate animals, there was no evidence of tremors at any stage and the convulsive threshold was further reduced, by about 32% compared to controls.

A simple interpretation of these results is that there is a locus for fine tremor in the midbrain under cortical inhibitory control; a second, different locus for coarse tremor also in the midbrain

† 1 atm = 101 325 Pa.

but without cortical inhibitory control; and a purely convulsive locus, caudal to the collicular region, which is subject both to cortical and, to a lesser extent, midbrain inhibitory control.

While alternative explanations can be invoked for the absence of tremors in the decerebrate animal, for instance that they may be masked by some mechanism arising as a result of decerebrate rigidity, it is clear that although the cortex is not essential for the expression of h.p.n.s., it exerts a pronounced inhibitory influence.

The role of monoamines

The role of brain biogenic amines in high pressure seizures was first suggested by Brauer *et al.* (1978), who showed that reserpine reduced the threshold pressure for convulsions in CD-1 mice. Subsequent studies (Koblin *et al.* 1980), with pharmacological agents that selectively depleted these monoamines, showed that reduction of central noradrenalin levels by FLA-63, a dopamine-β-hydroxylase inhibitor, likewise decreased the thresholds for high pressure convulsions. More recently, the actions of the monoamine neurotoxins 6-hydroxydopamine (6-OHDA), 5,6- and 5,7-dihydroxytryptamine (5,6-DHT, 5,7-DHT), which produce a physical destruction of monoaminergic neurons (Jonsson 1980), have also been investigated on high pressure convulsions in mice (Bowser-Riley *et al.* 1982). It was found that intracerebral injections of these neurotoxins lowered the h.p.n.s. thresholds in a similar way to the decorticate procedure (see table 1). The results of these investigations, together with those of reserpine, are summarized in table 2. An analysis of the monoamines depleted by these agents suggested that their actions are linked to a reduction in noradrenalin. That this action could be solely attributed to the depletion of noradrenalin is reinforced by the finding that desmethyliprimine (DMI), which prevents the neurotoxic action on noradrenergic neurons (Jonsson 1980), reverses the potentiating effect on the response to pressure.

TABLE 2. SUMMARY OF MONOAMINE–HIGH PRESSURE INTERACTIONS

drug	changes in h.p.n.s. thresholds			monoamines depleted
	fine tremor	coarse tremor	convulsions	
Reserpine	lowered	lowered	lowered	DA, NA, 5-HT
6-OHDA	lowered	no change	lowered	DA, NA
5,6-DHT	lowered	no change	lowered	5-HT, NA
5,7-DHT	lowered	no change	lowered	5-HT, NA
5,7-DHT with DMI	no change	no change	no change	5-HT

The action of noradrenalin in high pressure convulsions may, therefore, be similar to that seen in other seizure states in which it has been suggested that noradrenalin inhibits the spread of seizure activity within the brain (Jobe *et al.* 1973). This inhibitory action of noradrenalin has been shown to be limited to its terminal regions within the cortex and midbrain (Mason & Corcoran 1979). That this may also be true for high pressure convulsions is suggested by the similar effects of decortication and treatment with neurotoxins on h.p.n.s.

The experiments described do not support the idea of a direct cortical effect of pressure facilitating convulsive events at some sub-cortical site, although it is difficult to exclude such an action completely. It is known, however, that pressure does not change the levels of whole brain amines (Daniels *et al.* 1981), and the raising of brain amine levels, by L-dopa treatment (Halsey & Wardley-Smith 1981; Bowser-Riley *et al.* 1982) or by monoamine oxidase inhibitors

(Brauer 1975) gives no protection against h.p.n.s. Our working hypothesis has been, therefore, that pressure has little effect on cortical function, but that the cortex provides a substantial measure of inhibition to counter the convulsive activity that arises from the sub-cortical sites.

DRUG INTERACTIONS AND THE POSSIBLE ROLE OF AMINOACIDS

The sub-cortical site of the convulsant action of pressure is analogous anatomically to the known sites of action of the convulsant poisons strychnine and picrotoxin (see Sollmann 1957). The action of strychnine is thought to arise as a result of its ability to antagonize the actions of the inhibitory amino acid transmitter glycine, whereas that of picrotoxin is thought to result from the antagonism of the inhibitory action of γ-aminobutyric acid (GABA). (Eccles 1964; Schmidt 1971).
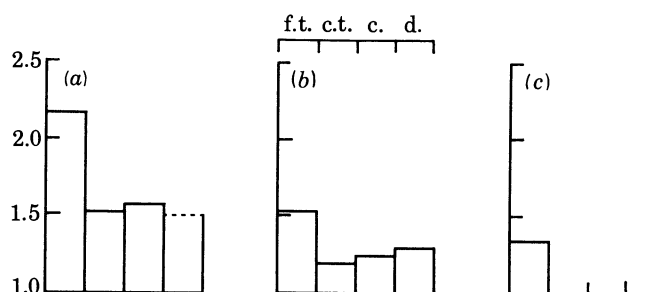

FIGURE 1. Relative changes in h.p.n.s. thresholds for the actions of some GABA related compounds compared to the appropriate drug vehicle control. Only statistically significant changes ($p < 1\%$) are shown (a) valproate (800 mg/kg); (b) flurazepam (20 mg/kg); (c) baclofen (10 mg/kg). Abbreviations: f.t., fine tremor; c.t., coarse tremor; c., convulsions; d., death.

Relation to GABA

An interaction with GABAergic mechanisms is suggested by the evidence that agents which potentiate the actions of GABA protect against the convulsive actions of pressure. The benzodiazepines, diazepam (Gran *et al.* 1980) and flurazepam (Bichard & Little 1981, 1982a), have been shown to significantly postpone high pressure convulsions. Bichard & Little also demonstrated that a substantial degree of protection was conferred by sodium valproate, amino-oxyacetic acid and di-aminobutyric acid. In addition, they established a positive correlation between the ability of these compounds to oppose the effect of pressure with their ability to antagonize seizures elicited by the GABA antagonist bicuculline. The actions of sodium valproate and flurazepam have been evaluated under our conditions, and the results are illustrated in figure 1. Valproate gives good protection to all aspects of h.p.n.s.; it increases the fine tremor threshold by a factor of 2.2 and the thresholds for coarse tremor and convulsions by about 1.5. The death threshold (figure 1) is shown as an estimate because it was normally in excess of 200 atm, compared to about 130 atm for controls. Flurazepam is rather less effective, with the maximum effect shown in figure 1. The threshold for fine tremor was increased by a factor of 1.5 and those for coarse tremor and convulsions by about 1.2. The action of flurazepam has been linked to specific diazepam receptors because its protective action can be readily reversed by the benzodiazepine antagonist RO-15-1788 (Bichard & Little 1982b). The effect of baclofen, an antispastic agent and centrally acting muscle relaxant (Cutting & Jordan 1975), on the response to pressure, it also shown in figure 1. Baclofen, although synthesized

as a GABA analogue, does not antagonize the convulsive effect of bicuculline and similarly has very little effect on h.p.n.s. This may support the suggestion that the facilitation of GABA-ergic transmission opposes the effects of pressure (Bichard & Little 1981, 1982*a*).

Relation to glycine

A possible role for glycine arose from our studies into the effects of a group of mephenesin-like muscle relaxants on the response to pressure. The mode of action of these compounds is generally accepted to be mediated at a sub-cortical level, involving polysynaptic pathways. Although they are not usually regarded as anticonvulsants they are known to be effective antagonists of a variety of induced seizure states (Berger 1947; Smith 1965).

The actions of the centrally acting muscle relaxants on h.p.n.s. are shown in table 3 and their relative effectiveness in figure 2. The muscle relaxants were injected intraperitoneally at doses calculated to give equivalent clinical effects, on the basis of a 15 min loss in righting reflex. It was found that mephenesin, a phenyl substituted propandiol, significantly increased the pressure of onset for all four behavioural end points associated with h.p.n.s. The monocarbamate analogue of mephenesin, methocarbamol, although less potent, afforded a similar degree of protection. The action of mephenesin and methocarbamol together appeared to be simply additive, indicative of a common site of action. Tests with chloro- and napthyl-derivatives showed a similar profile, which suggests a consistent potency of the mephenesin structure against all aspects of h.p.n.s. The generalized effect was to raise the thresholds by a factor of 2.5 for tremors and 1.5 for convulsions and death.

The relative effectiveness of mephenesin and methocarbamol on the different components of the h.p.n.s. (figure 2) clearly shows their protective action is most marked on the early stages of h.p.n.s. This could reflect the known short duration of action of these compounds. However, the ethandiol derivative, styramate, a more potent and longer acting muscle relaxant (Witkin *et al.* 1960) postponed the convulsions by the same extent as mephenesin, but was much less effective in controlling tremors. Two additional muscle relaxants, meprobamate and cariso-prodol, were tested for their effectiveness against h.p.n.s. Both are aliphatic dicarbamate derivatives of mephenesin and, like styramate, are more potent and longer acting than mephenesin in muscle relaxation (Berger 1954, 1959). However, both meprobamate and carisoprodol gave very different results. Meprobamate postponed the onset of h.p.n.s. from a control value of 35 to 58 atm, and elevated the death threshold to 167 atm, but in addition, drastically changed the nature of the response. This change was characterized by the sudden onset of severe tremors culminating in violent continuous myoclonic seizures. In contrast, carisoprodol, while marginally increasing the threshold for fine tremor, had no discernible effect on either the nature or the onset pressures of the other end points of h.p.n.s.

Interactions between h.p.n.s. and analeptics

It is instructive to compare the action of the centrally acting muscle relaxants on h.p.n.s. with their actions in opposing other induced seizure states (Smith 1965). Mephenesin and methocarbamol are both strong antagonists of the convulsions and lethality of strychnine. On the other hand, although meprobamate gives good protection against the lethality of strychnine, it is a poor antagonist of strychnine convulsions. Carisoprodol has very little effect on either aspect of strychnine toxicity. Additional experiments with the related anti-spasmodic
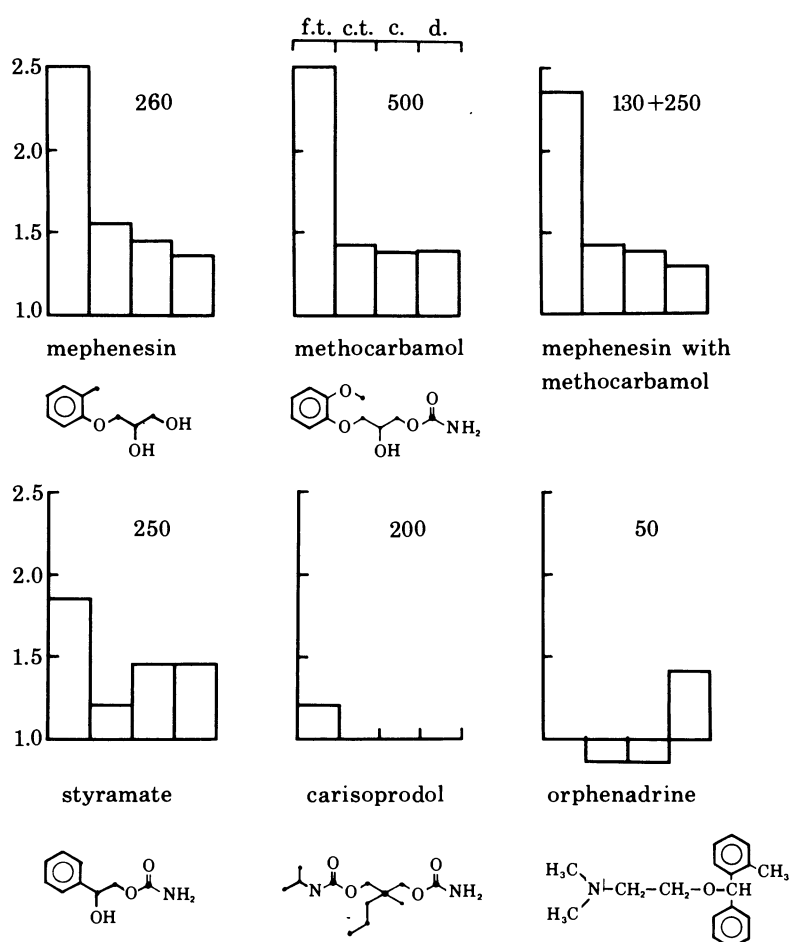
FIGURE 2. Relative changes in h.p.n.s. thresholds for the actions of some mephenesin related muscle relaxants and antispasmodics compared to the appropriate drug vehicle control. Only statistically significant changes ($p < 1\%$) are shown. Abbreviations: f.t., fine tremors; c.t., coarse tremors; c., convulsions; d., death. The concentration/(mg/kg) is given on each graph.

TABLE 3. H.P.N.S. THRESHOLDS ($\pm$ S.E.)/ATM FOR CD-1 MICE TREATED WITH MEPHENESIN-LIKE MUSCLE RELAXANTS

drug	concentration mg/kg	fine tremor	coarse tremor	convulsions	death	number
vehicle control	—	35 ± 1	72 ± 1	83 ± 1	118 ± 2	15
mephenesin	260	87 ± 3	110 ± 2	120 ± 2	160 ± 3	10
methocarbamal	500	86 ± 4	102 ± 2	116 ± 2	167 ± 5	6
mephenesin with methocarbamol	{ 130 250	82 ± 2	102 ± 1	115 ± 2	153 ± 6	11
meprobamate	200	$58\pm2\dagger$	$\dagger$	$\dagger$	167 ± 1	12
styramate	250	65 ± 1	86 ± 1	120 ± 1	171 ± 6	6
carisoprodal	200	42 ± 2	75 ± 1	90 ± 4	139 ± 4	6
orphenadrine	50	40 ± 2	63 ± 1	73 ± 1	168 ± 7	6

$\dagger$ Onset of severe tremors leading to continuous convulsions.

orphenadrine, which is ineffective against strychnine seizures (Chronheim 1958), demonstrated that this compound, like carisoprodol, failed to give protection against h.p.n.s. (see figure 2). There is, therefore, a considerable similarity between h.p.n.s. and strychnine in the susceptibility, or resistance, of their action to a range of relaxant drugs.

The significance of this parallelism is increased by the fact that it is absent if another chemical convulsant is chosen for the comparison. Thus, with metrazol-induced seizures, the order of effectiveness is reversed; carisoprodol and meprobamate affording better protection
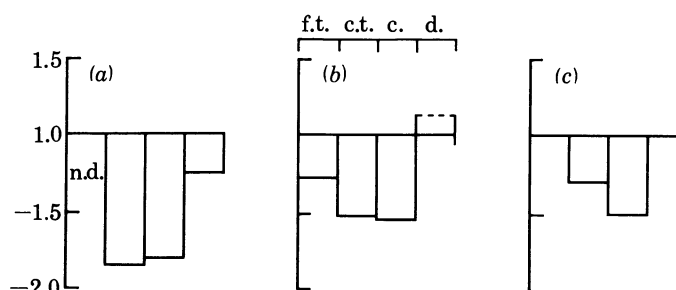

FIGURE 3. Relative changes in h.p.n.s. thresholds for the actions of three convulsants compared to the appropriate vehicle control. Only statistically significant changes ($p < 1\%$) are shown (a) Strychnine (1.0 mg/kg): (b) picrotoxin (3.0 mg/kg); (c) metrazol (40 mg/kg). Abbreviations: f.t., fine tremors; c.t., coarse tremors; c., convulsions; d., death; n.d., not determined (see text).

TABLE 4. H.P.N.S. THRESHOLDS ($\pm$S.E.)/ATM FOR CD-1 MICE TREATED WITH CONVULSANTS

drug	concentration mg/kg	fine tremor	coarse tremor	convulsions	death	number
vehicle control	—	36 ± 1	72 ± 1	88 ± 1	131 ± 2	36
strychnine	1	*	39 ± 1	49 ± 3	105 ± 6	6
picrotoxin	3	28 ± 1	47 ± 3	57 ± 6	149 ± 9	6
metrazol	40	33 ± 2	56 ± 1	59 ± 3	137 ± 11	6
untreated control	—	35 ± 1	73 ± 1	87 ± 1	129 ± 4	14

* Not determined; see text.

than either mephenesin or methocarbamol. It is this parallelism that suggests that pressure may specifically affect glycine-mediated inhibitory pathways. If this were so, it might be expected that strychnine would potentiate h.p.n.s. more readily than do other analeptics not involving glycine.

The experiments shown in table 4 and summarized in figure 3, test this point. Strychnine, picrotoxin and metrazol were given intraperitonally at a dose calculated as the highest compatible with the failure to elicit convulsions in mice exposed to an O_2 pressure of 1 atm for 1 h within the pressure vessel.

Strychnine proved to be both the most potent and the most efficacious, and while it was not possible to distinguish the fine tremor induced by pressure from those resulting from the actions of strychnine alone, the thresholds for coarse tremor and convulsions were dramatically reduced. That there was a true facilitation of h.p.n.s. was suggested by the fact that the convulsions observed were characteristic of h.p.n.s. and were clearly distinguishable from the tonic extensor spasms provoked by convulsive doses of strychnine. Picrotoxin moderately lowered the threshold for fine tremors, markedly lowered the thresholds for coarse tremors and

convulsions and gave rise to a small but not significant increase in the death threshold. Metrazol, although least potent, similarly lowered the thresholds for coarse tremors and convulsions, but failed to have any effect on the thresholds for fine tremors and death.

The finding that strychnine potentiates h.p.n.s. suggests that the anti-h.p.n.s. and anti-strychnine action of mephenesin may share a similar mechanism. So, it may be that the convulsive effects of high pressure arise as a result of some action on the inhibitory processes mediated by glycine. However, the fact that both metrazol and picrotoxin potentiate h.p.n.s., though to a lesser extent than strychnine, indicates that the action of pressure is not expressed exclusively via an action on the glycine pathways. The action of these convulsants is thought to be mediated via GABA and it has been clearly established that GABA potentiating agents also possess anti-h.p.n.s. actions. Therefore, it might be plausible to suggest that the actions of pressure, in common with strychnine and picrotoxin, produce convulsions at a sub-cortical site by depressing inhibition. However, there is to date no evidence that fully excludes the alternative possibility that pressure actually gives rise to convulsions by an intensification of excitatory processes.

CONCLUSIONS

High pressure elicits a wide variety of effects, but the approach used in this paper has been to focus particularly on the convulsant effect, as it was considered likely to be the most profitable. It is true that various other behavioural signs can be differentiated from the convulsions, as the work reported illustrates. The view has been taken, however, that they are all manifestations of a similar neuronal hyperexcitability in response to pressure, and that they may indeed represent a progression of effects, which culminate in convulsions.

The neuroanatomical studies have shown that pressure has a subcortical site of action, and that the cortex provides a substantial measure of inhibition to counter the convulsions that arise from the sub-cortical sites. The interaction between pressure and the monoamine transmitters, when taken together with the results of the neuroanatomical studies, have suggested that pressure has no direct cortical action, and that the descending inhibition originating from the cortex is dependent on noradrenalin.

The pattern of actions of the various pharmacological agents that oppose the effects of pressure, when compared with their ability to antagonize other sub-cortically induced seizures, not only reinforce the finding that high pressure convulsions arise in sub-cortical structures, but also may give some indication of the mechanism by which the convulsions are initiated.

The clear division of action between the aromatic and aliphatic propandiols in opposing the effect of pressure has been shown to be related to the relative ability of either group to antagonize seizures induced by strychnine. Mephenesin is a potent antagonist of strychnine, an action which, like its effect against pressure, has been shown to be independent of its ability to produce muscle relaxation (Berger 1952). The finding that strychnine potentiates h.p.n.s. suggests that the anti-h.p.n.s. and anti-strychnine action of mephenesin may share a similar mechanism. On the basis that strychnine acts by blocking the inhibitory processes mediated by glycine, it has been suggested that the convulsive effects of high pressure may result from some action on these same processes.

There is a theoretical possibility that the effects of pressure are mediated exclusively by an action on glycine related pathways; but it must be remembered that the GABA antagonist, picrotoxin, potentiates h.p.n.s., and that GABA-mimetics also possess anti-h.p.n.s. properties,

so that GABA-ergic pathways may also be involved. It is futher possible that pressure does not in fact specifically perturb the action of either of these inhibitory transmitters but affects some aspect of the inhibitory mechanism that is common to both.

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Discussion

H. J. Little (*University Department of Pharmacology, Oxford, U.K.*). When we originally showed that sodium valproate and flurazepam gave protection against the h.p.n.s. (Bichard & Little 1982 a), we chose these drugs because they had been demonstrated to potentiate central γ-aminobutyric acid transmission. Is there any electrophysiological evidence to show that the muscle relaxants used by Dr Bowser-Riley in his experiments alter glycine transmission?

F. Bowser-Riley. Unfortunately, the extensive investigations into the mode of action of the mephenesin-related muscle relaxants (see the review by Smith 1965) pre-date the suggestion that glycine has an inhibitory transmitter role within the central nervous system (Werman et al. 1967). However, given the dearth of agents available that may be directly associated with the putative neurotransmitter role of glycine, and given the evidence about strychnine, the hypothesis that mephenesin-related muscle relaxants are so associated appears well worth investigation. It is possible that these agents indirectly act to facilitate the actions of glycine in a manner analogous to that suggested to account for the actions of benzodiazepines and sodium valproate in their facilitation of central GABA transmission.

Reference

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R. W. Brauer (*Institute of Marine Biomedical Research, Wilmington, U.S.A.*). I believe that the discussion of the role of animal experimentation in relation to development of undersea medicine calls for additional comment. I feel that all too often a healthy interaction between scientists engaged in animal experimentation and their colleagues engaged in conducting human studies is not as productive as it should be. The job of the animal experimenters is to point out new phenomena, to try to define mechanisms, to assess possible interactions, and to explore possibly dangerous consequences of one or another course of action. It should be the role of human experimenters to translate these findings to general strategies for use with human subjects and to devote their attention to estimating numerical values of operating parameters allowing human diving operations to proceed with safety and with maximum efficiency. At a time when it seems clear to me, and to a number of others in this field, that we may well be skirting the edge of serious potential dangers, the numbers of human subjects subjected to such experimental procedures should be limited as far as possible. Unless the results of animal experiments are utilized to the full, it appears that unnecessary and ethically questionable hazards to the human subjects are entailed in such experimentation. The crux of the matter is that every animal study has demonstrated high degrees of individual variability in the susceptibility of mammals to hydrostatic pressure effects. Nothing in the human experience indicates that man is an exception to this rule. So, experiments designed to probe the response

of mammals, including man, to any specific aspect of high pressure exposures must be subject to the rules of statistical inference and proper design of experiments that have been laboriously worked out by pharmacologists and physiologists over the last 50 years. These would, for instance, proscribe attempts to make a choice between two related drugs on the basis of experiments involving a very limited number of subjects in a multi-celled design trying to respond simultaneously to many experimental variables, and to do so in experiments replicated an insufficient number of times. Yet, this is precisely what the inherent risk and cost in money and in effort of manned deep diving experiments imposes upon us. Examples of the consequences of this peculiarity of our field are easy to find, for example, the present uncertainty as to the most favourable gas mixture to use, or indeed whether to use anything other than heliox at all, or the uncertainty with regard to even the most general shape of the desirable compression curves for particular high pressure exposures, which have been mentioned in this symposium. In all of these cases, therefore, the questions of principle can and should be decided on the basis of animal experiments, and the task of the human experiment should be then to apply those conclusions to optimization of procedures, and to tests that can only be conducted with man as a subject, and which ultimately address the question of how well a given subject can function under a given set of compression and environmental conditions during an actual dive.