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EFFECTS OF KETAMINE AND OF HIGH PRESSURE ON THE RESPONSES TO γ-AMINOBUTYRIC ACID OF THE RAT SUPERIOR CERVICAL GANGLION *in vitro*

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1 The method of Brown & Marsh (1974) for recording of surface potentials from the rat superior cervical ganglion has been adapted for use in a high pressure chamber in order to study the effects of high pressure of helium and the possible interactions with the effects of general anaesthetics.

2 Helium pressure of 130 atm did not alter the amplitude of the responses recorded from the ganglion in response to γ-aminobutyric acid (GABA) application (9.7 and 19.4 μM) but the amplitude of responses to a nicotinic agonist were depressed.

3 Ketamine, at concentrations between 18 and 180 μM, considerably potentiated the responses of the ganglion to GABA.

4 Helium pressure (130 atm) did not reverse the potentiation of GABA by ketamine.

5 The results are discussed in connection with the ability of ketamine to oppose the behavioural effects of high pressure.

Introduction

It has been known for the past decade that the behavioural effects of high pressure and of general anaesthetics are antagonistic. Pressures of the order of 100 atmospheres (atm), applied using helium or hydrostatic pressure, reverse the general anaesthesia due to a wide variety of compounds (Lever, Miller, Paton & Smith, 1971; Halsey & Wardley-Smith, 1975; Miller & Wilson, 1978). The high pressure neurological syndrome (HPNS), a hyperexcitability state characterized by tremors and convulsions, is seen in mammals at between 30 and 100 atm. General anaesthetics postpone the onset of these behavioural signs to higher pressures, although this action correlates poorly with general anaesthetic potency (Green, Halsey & Wardley-Smith, 1977). It has been suggested that the physiological sites of pressure reversal of anaesthesia and of the origin of the HPNS are not identical (Miller, Wilson & Smith, 1978; Smith, Smith, Eger, Halsey & Winter, 1979). Several theories based on the physiochemical properties of general anaesthetics and involving non-specific actions on cell membranes have been put forward to explain the phenomena (Miller, Paton, Smith & Smith, 1973; Miller, 1977; Trudell, 1977; Halsey, Wardley-Smith & Green, 1978), but little is known about the underlying physiological changes at the 'sites' described. The effectiveness of general anaesthetics against the HPNS does not show a simple correlation with lipid solubility as has been demonstrated for general anaesthetic potency and so it is possible that properties in addition to their non-specific actions on cell membranes may be involved. Information concerning the changes in neuronal transmission, which occur under these conditions, would be useful not only from a theoretical point of view, but may also have future applications in deep sea diving, where the initial stages of the HPNS are a problem. Ketamine was selected for use as a general anaesthetic in the present studies because it has been shown to be particularly effective against the HPNS (Green *et al.*, 1977).

Studies of the effects of high pressure on synaptic transmission are at an early stage (for review, see Wann & Macdonald, 1980). It is known that pressure can slow ion channel opening during axonal conduction (Henderson & Gilbert, 1975), but little is known of its effects on vertebrate synapses, especially those which use transmitters other than acetylcholine.

Recently we have shown (Bichard, Little & Paton, 1981; Bichard & Little, 1982) that drugs which facilitate γ-aminobutyric acid (GABA) transmission are effective against the HPNS. This has led us to investigate the effects of pressure on GABA transmission *in vitro* and the interactions between the effects of pressure and of the general anaesthetics.

The experiments presented here are concerned with the effects of pressure on the depolarizing responses of the rat superior cervical ganglion. Al-

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though GABA transmission is not thought normally to occur in the ganglion, this tissue contains receptors which resemble closely those in the CNS (Bowery & Brown, 1974). Recording neuronal responses to added drugs enabled analysis of the effects of pressure and of anaesthetics on these without the complication of presynaptic changes.

A preliminary account of these results was presented at the British Pharmacological Society Meeting at Oxford, September 1981.

Methods

The method of Brown & Marsh (1974) for recording of changes in ganglion surface potential has been adapted for use inside a pressure chamber. The apparatus (Figure 1) is entirely self-contained and enables superfusion of the preparation, automatic addition of drugs and recording of responses for up to 2.5 h. The internal volume of the pressure chamber was 2.6 l.

The electrodes used were Ag/AgCl in 3 M KCl. Tests were made to determine whether or not helium pressure affected the recording system. For these tests a piece of cotton was perfused with Krebs solution in the same way as the ganglion and square wave pulses of the same amplitude and duration as the agonist responses were applied via Ag/AgCl stimulating electrodes. The responses of the electrodes to these test pulses were unaffected by the application of up to 130 atm of helium. These tests were carried out on several pairs of electrodes, at intervals during the experiments. New electrodes had to be made for each experiment because the decompression procedure resulted in gas bubble formation. No changes were seen in the resistance of the electrodes at pressure.

In the majority of experiments the ganglia were dissected out the day before and kept at 0.4°C overnight. This provides a more stable baseline for recording (Brown & Galvan, 1977). Comparison using freshly dissected tissues showed that this procedure did not affect the results. The tissues were perfused with standard Krebs solution at 1 ml min^{-1} and the chamber was flushed initially for 1 min with 95% O_2 plus 5% CO_2. The perfusion rate was measured at atmospheric pressure and at 130 atm helium and no changes were seen. The pH changes in Krebs solution on application of this order of pressure have been measured by Kendig, Trudell & Cohen (1975) and found to be not more than 0.2 pH unit.

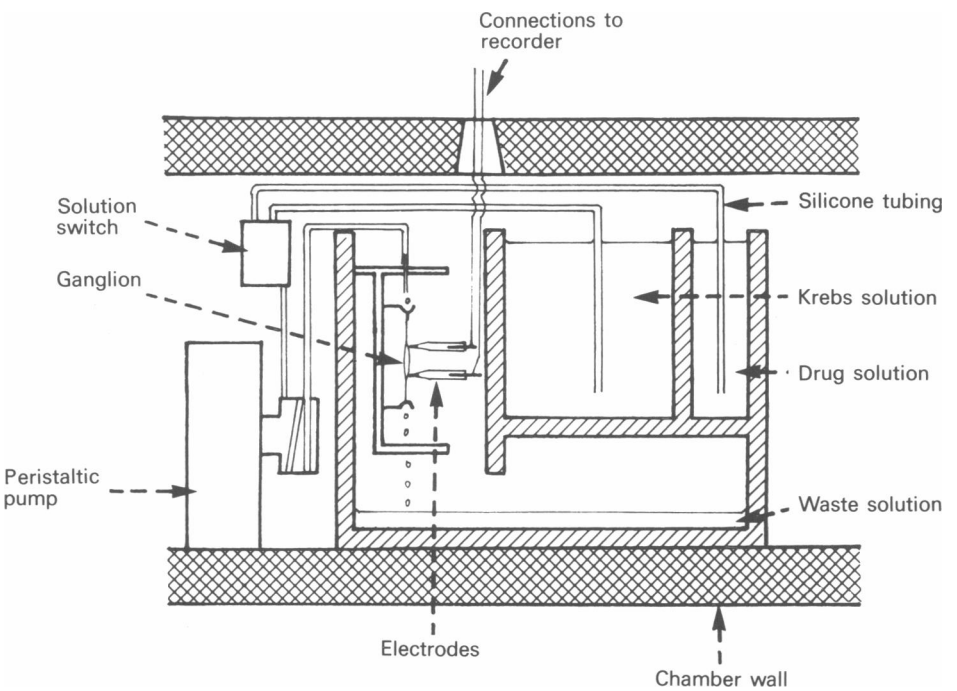

Figure 1 Apparatus used for extracellular recording inside a pressure chamber. The tissue was continuously superfused with Krebs solution and agonist drugs applied, in this solution, for 2 min in every 15 min. Recording was by Ag/AgCl electrodes connected to a Tekman flat-bed recorder. Helium was added directly from cylinders and chamber pressure measured with a bourdon gauge.

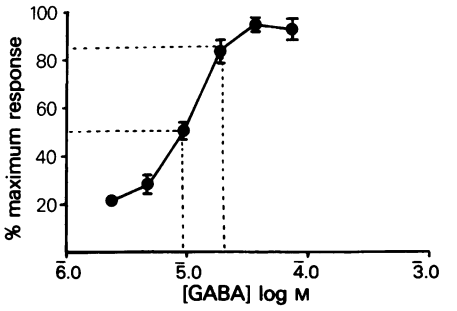

Figure 2 Dose-response curve to γ-aminobutyric acid (GABA) obtained in separate experiments outside the pressure chamber. The ED_{50} and ED_{85} concentrations were established from this curve as indicated. The doses of GABA were applied at 15 min intervals. Mean values with s.e.mean (vertical lines) are shown ($n = 4$).

The temperature within the chamber was monitored throughout the experiments on the pen recorder and maintained at 27°C ± 0.5°C. The temperature changes during pressurization were kept within 1°C of 27°C. Helium was applied directly from cylinders and pressure measured on a bourdon gauge. The small chamber size restricted the application of GABA doses to one concentration per experiment. From separate experiments outside the pressure chamber, a dose-response curve to GABA was established and the ED_{50} and ED_{85} concentrations measured (i.e. those concentrations which produced 50% and 85% respectively of the maximum response) (Figure 2). The mean amplitude of the maximum response obtained was 787 μV ± 66 μV (s.e.mean). These concentrations were chosen for study of the effects of pressure and of ketamine. In each experiment a dose of the chosen concentration of GABA was applied at 15 min intervals, the drug contact time being 2 min. Control experiments showed that responses of consistent amplitude could be obtained from the tissues for many hours using this regime. In each experiment a minimum of three consecutive, steady, control responses was obtained before pressure was applied. Pressurization took 5 min and the doses of agonists were then repeated up to six times, beginning from 15 min after the start of the application of pressure. When ketamine was used it could not be added after the chamber was closed so steady responses in the presence of ketamine were obtained with the apparatus outside the chamber, the apparatus moved inside, the chamber door fastened, and steady control responses again obtained before the helium pressure was applied. The effects of decompression on the responses obtained could not be studied because of the formation of bubbles in the tubing and the electrodes.

The standard pressure chosen for investigation was 130 atm of helium as this causes convulsions and death in small mammals (Brauer, Mansfield, Beaver & Gillen, 1979) and also reverses general anaesthesia.

Ketamine hydrochloride was obtained from Parke-Davis & Co.

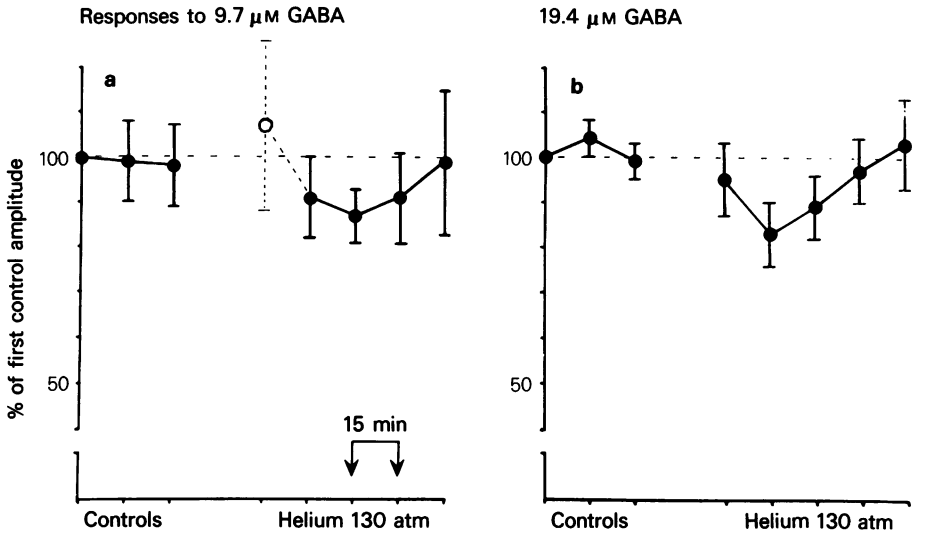

Figure 3 Effects of helium pressure on the responses of the ganglion to GABA, at (a) ED_{50} (9.7 μM) and (b) ED_{85} (19.4 μM). The results are expressed as percentages of the first control response; values are mean of $n = 7$ (a) and $n = 8$ (b); vertical lines show s.e.mean. Three (consecutive) steady control responses were recorded before the application of helium pressure, to 130 atm over 5 min. The dotted line indicates that results at this time were obtained in only four experiments.

Helium was obtained from the Physical Chemistry Laboratory helium plant, Oxford University, purity 99.995%.

The composition of Krebs solution was as follows (mM): NaCl 118, KCl 4.75, $CaCl_2$ 2.55, $MgSO_4$ 1.2, KH_2PO_4 1.19, $NaHCO_3$ 25 and D-glucose, 11.

Results

The application of helium pressure (130 atm) caused little change in the responses of the ganglia to GABA (Figures 3 and 4). The results in Figure 3 are presented as percentages of the first response so that mean values and standard errors could be obtained to give an indication of the variation of both controls and responses obtained under pressure. Analysis of variance was carried out on the original data and showed that, in total, the GABA response amplitude was not significantly altered by pressure ($P > 0.05$) ($n = 7$ for 9.7 μM GABA and $n = 8$ for 19.4 μM GABA). Figure 4 shows an original tracing from one of these experiments. The baseline of the recordings shifted on application of the helium pressure but returned to the original level during or immediately after pressurization. The d.c. drifts have been observed previously when pressure was applied to recording systems (Hills, 1969) and so the effect seen was more likely to have been due to an effect on the electrode processes than on the tissue. The baseline remained steady at pressure once it had settled. Small changes in the background noise on the recordings after pressurization could be attributed to a mechanical effect from the drops of Krebs solution passing over the electrodes. In some early experiments the first response after pressurization was not clear and these results have not been included in Figure 3, hence the dotted line, but as the technique was improved this did not cause problems in later experiments.

It was found that the responses to a selective nicotinic agonist phenoxyethyltrimethylammonium chloride (PE, 'phenethylcholine') were decreased to approximately 70% of control values by this helium pressure. Figure 5 shows an example of the effects of pressure, in this case on the ED_{85} concentration of phenethylcholine (this concentration was established in separate experiments as that which caused re-

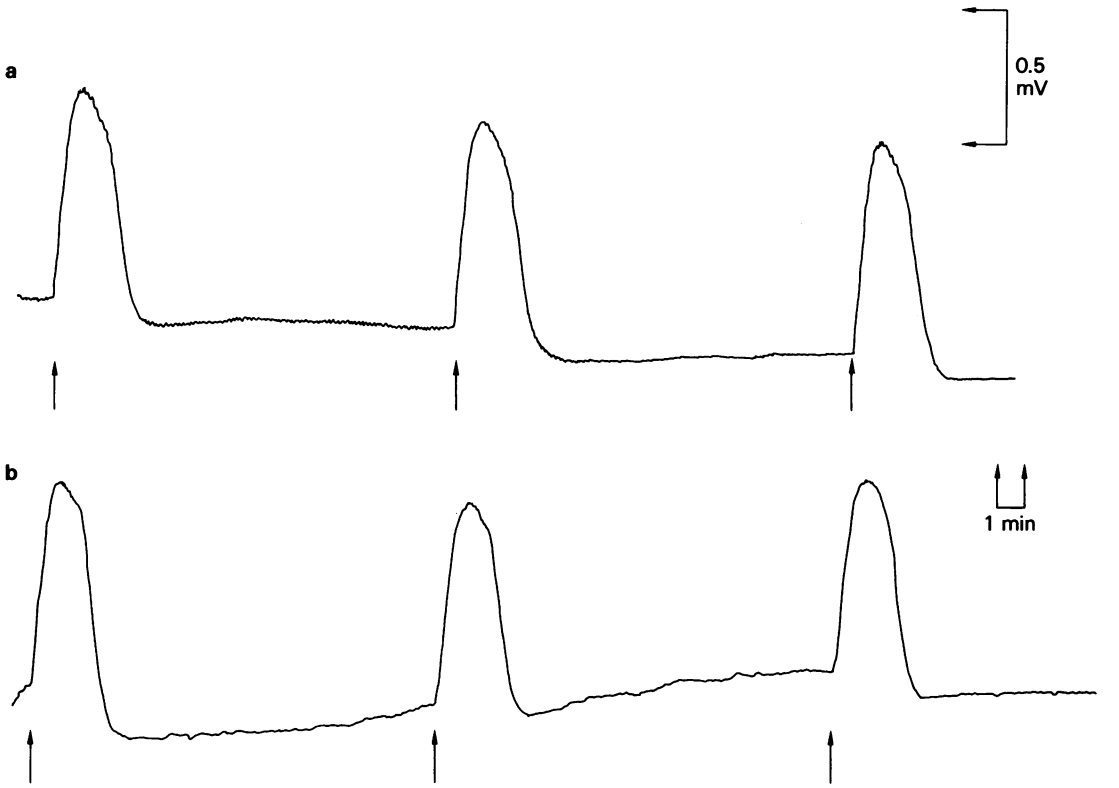

Figure 4 Example of traces obtained during one experiment in the study of the effects of helium on responses to GABA, ED_{85}. The doses of GABA (each 19.4 μM at arrows) were applied at 15 min intervals. Three control responses were obtained at normal pressure (a) before the application of helium at 130 atm (b).

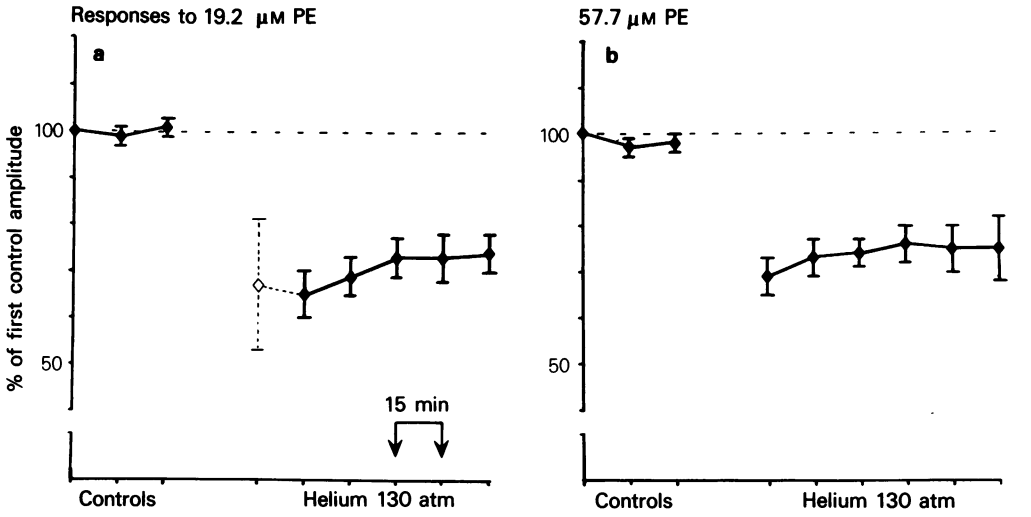

Figure 5 The effects of pressure on the ED_{85} concentration of phenethylcholine (PE), a nicotinic agonist. The results are expressed as percentages of the first control response, and are the mean of $n = 9$ (a) and $n = 7$ (b); vertical lines show s.e.mean. Three (consecutive) steady control responses were recorded before the application of helium pressure, to 130 atm over 5 min.

sponses with a mean amplitude of 85% of the mean maximum response). The number of tissues used in these pressure experiments was seven and the mean amplitude of response to the ED_{85} was 1.3 ± 0.3 mV.

At normal atmospheric pressure ketamine was found to increase considerably the amplitude of the responses to GABA (Figure 6) ($n = 6$). This potentiation was seen with concentrations of ketamine as low as 18 μM, increased to a maximum at about 180 μM then declined as the concentration was increased further. The concentration of 180 μM was therefore chosen for further investigation.

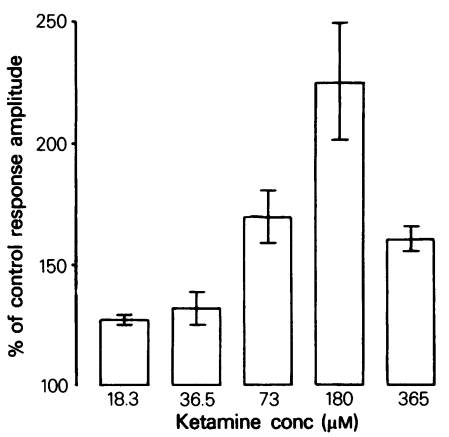

Figure 6 The effects of ketamine on the responses of the ganglion to GABA 9.4 μM (ED_{50}). The results are expressed as percentages of the initial control response amplitudes. The doses of GABA were applied at 15 min intervals and the effects of ketamine measured at 30 min after its addition to the superfusing Krebs solution. Values are mean of $n = 6$; vertical lines show s.e.mean.

In view of the effectiveness against the HPNS of the drugs which facilitate GABA transmission (see Introduction) it was of interest to determine whether a similar action of ketamine might contribute to its actions against the HPNS. In order to investigate this fully, it is necessary to know whether the facilitation of GABA responses induced by ketamine occurs in the CNS and also whether or not the effect is reversed by pressure, as are the nonspecific effects of general anaesthetics *in vivo*. It is not yet possible to carry out recordings from vertebrate CNS preparations under pressure which could provide this information. As a preliminary step we decided to investigate whether pressure affected the increases in the responses of the ganglion to GABA which we found with ketamine.

Figures 7 and 8 shows that, overall, helium did not change the amplitude of the responses to GABA in the presence of ketamine. As explained in the Methods section, control responses in the presence of ketamine were re-established in the chamber before pressure was applied. Figures 7 and 8 show these latter responses with ketamine and then the effects of pressure ($n = 6$). There was a small decrease in the GABA responses 15 min after the start of pressurization but this was not seen at later times. When the amplitude of the responses at this 15 min time interval were compared with the control values immediately before, the decrease was found to show significance ($P < 0.05$) but when analysis of variance was used to compare all the control values with all the responses at pressure no significant changes were

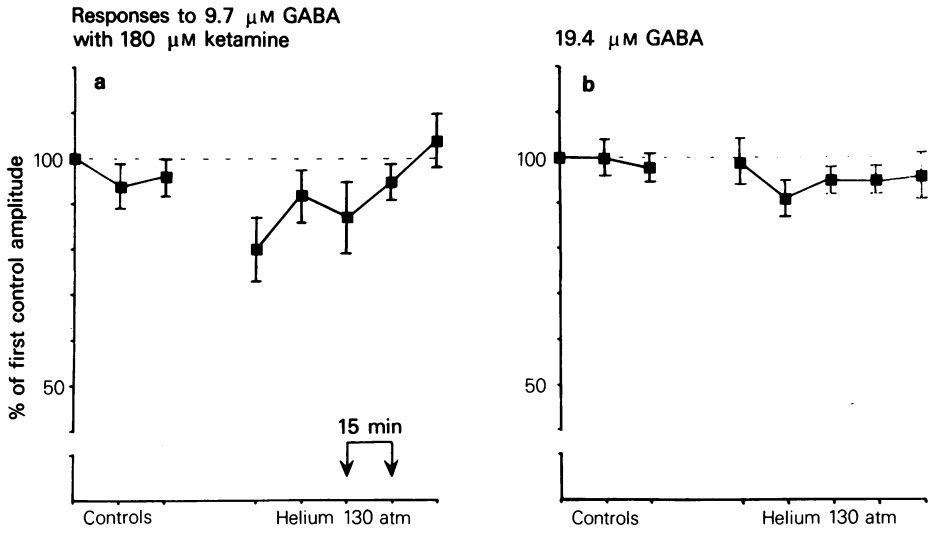

Figure 7 The effects of helium pressure on the responses of the ganglion to GABA after the addition of ketamine 180 μM. The effect of ketamine on the responses are not shown in this figure because the apparatus has to be moved into the pressure chamber after the addition of ketamine. Responses in the presence of ketamine were therefore reestablished in the chamber before the addition of helium pressure. 'Controls', therefore, refers to the steady responses obtained in the pressure chamber, after the addition of ketamine, but before the application of helium. The results are expressed as percentages of the amplitude of the first of these responses. When three steady responses had been obtained helium was applied, to 130 atm in 5 min.

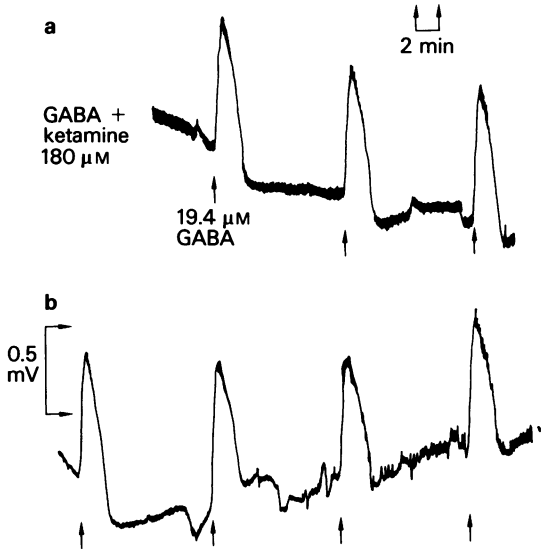

Figure 8 Example of the traces obtained in one experiment in the study of the effects of helium pressure (130 atm) on the responses of the ganglion to GABA after the addition of ketamine (a), then helium pressure was applied and the recording continued (b).

seen ($P>0.05$). The decrease at 15 min was not sufficient to reverse the effect of ketamine as this concentration more than doubled the response amplitude.

Discussion

The results show that 130 atm of helium pressure did not alter the responses of the ganglion to GABA, although the nicotinic responses were depressed. The latter finding is in agreement with the results of other workers using stimulation of the preganglionic nerve (Kendig *et al.*, 1975). It is possible that pressure depressed both the responses to GABA and the glial uptake mechanism which is present in ganglia but it seems unlikely that two effects such as this would have led to no net change at either concentration of GABA. (The possible contribution of changes in GABA uptake to the effect of ketamine is currently under investigation). The GABA receptors in the ganglia have been shown to produce the same increase in chloride conductance as occurs in the CNS at GABA-synapses (Adams & Brown, 1975). The recording of the responses as depolarization rather than hyperpolarization is thought to be due to the distribution of chloride ions across the membrane (Adams & Brown, 1975) and this type of response to GABA is also seen in recordings from the CNS.

Several studies on the effects of this order of pressure on synaptic transmission have reported a depressant action, for example in the squid synapse (Hendersen, Lowenhaupt & Gilbert, 1977) in crustacean synapses (Campenot, 1975) and in *Helix* neurones (Wann, Harper, Wilcock & Macdonald, 1977) but it has not been possible to separate clearly pre- and postsynaptic effects. The present results show that the postsynaptic responses to GABA do not follow this pattern. The molecular details of GABA binding and chloride conductance changes are not yet known but the explanation for the difference between the effects of pressure on GABA and on nicotinic responses may lie in the relative volume changes involved in the reactions of binding and conductance changes as, by Le Chatelier's principle, the smaller these are the less the effects of pressure are likely to be.

The method of recording used in the present experiments did not allow for observation of rapid changes in responses immediately on application of pressure. Comparison was made only between the steady states of recording at normal and at raised pressures.

The basis of the HPNS is still unknown, either at the anatomical or molecular level, but repetitive firing has been implicated (Kendig, Schneider & Cohen, 1978). Certain resemblances to other types of convulsions have been shown (Brauer, Beaver, Lahser, McCall and Venters, 1979; Koblin, Little, Green, Daniels, Smith & Paton, 1980) including those caused by decreases in GABA transmission (Bichard & Little, 1982), but the pattern of drug effects differs from other known hyperexcitable states. The evidence presented here suggests that depression of postsynaptic responses to GABA may not contribute to the syndrome, although the many dangers of extrapolation from isolated peripheral tissues to the CNS *in vivo* are recognized and the time course of the experiments may have precluded observation of some changes.

Potentiation of GABA transmission has been observed with many general anaesthetics, such as the barbiturates (Nicoll, 1977; Huang & Barker, 1980), although it is not clear whether or not it is a feature of all general anaesthetics. The concentrations in the present experiments at which ketamine was found to increase the amplitude of the responses of the ganglion to GABA (18–180 μM) are similar to those that have been measured in brain during general anaesthesia. For example, Cohen & Trevor (1974) showed that the plasma concentration of ketamine in rats 22 min after intravenous injection of 20 mg kg^{-1} ketamine hydrochloride was 81 μM. In addition, Cohen, Chan, Way & Trevor (1973) showed that the peak brain concentration of ketamine 0.5 min after intravenous injection of the above dose was 365 μM, reflecting the preferential accumulation of this drug in brain tissue. Prolongation of inhibitory postsynaptic conductance changes by ketamine was found by Scholfield (1980) using the olfactory cortex preparation but the concentrations then used were higher than in the present experiments (300 μM). Wood & Hertz (1980) found that ketamine increased the GABA content of brain fractions. This was attributed to inhibition of GABA uptake (mainly the neuronal mechanism), and it was suggested that this might contribute to the anti-convulsant effect of ketamine. As it has been shown (Bichard *et al.*, 1981; Bichard & Little, 1982) that drugs which facilitate GABA transmission are effective against the HPNS, we suggest that increases in the effectiveness and/or the concentration of GABA at the synapses may contribute to the actions of ketamine against the HPNS. This is suggested to occur in addition to its nonspecific actions and may constitute one of the 'sites' of action of general anaesthetics which have been discussed in current theories. Actions such as this may partially explain the findings that the effects of pressure and of general anaesthetics *in vivo* do not follow closely the predictions from physicochemical theories (Winter, Smith, Smith & Eger, 1976; Halsey *et al.*, 1978; Miller *et al.*, 1978).

The lack of reversal by pressure of the effect of ketamine on GABA seen in the present experiments has two implications. The possibility that this type of effect may contribute to its anticonvulsant effect at pressure *in vivo* is discussed above, but the lack of pressure reversal also provides an indication that this action is distinct from the site at which pressure reversal of ketamine anaesthesia occurs. Pressure has been shown to reverse the general anaesthesia *in vivo* produced by ketamine (Miller & Wilson, 1978) although there is some controversy about whether this reversal occurs to the same extent as with other general anaesthetics (Halsey *et al.*, 1978). This is difficult to determine without knowledge of the effects of pressure on the pharmacokinetics of ketamine. It may be that more than one effect of ketamine contributes to the loss of the reflexes which are used as endpoints in the experiments *in vivo*, and that not all of these changes are reversed by high pressure.

It may therefore be important to consider both the specific *and* the nonspecific actions of general anaesthetics in the analysis of their effects at high pressure.

References

ADAMS, P.R. & BROWN, D.A. (1975). Actions of γ-aminobutyric acid on sympathetic ganglion cells. *J. Physiol.*, **250**, 85–120.

BICHARD, A.R. & LITTLE, H.J. (1982). Drugs which increase GABA transmission protect against the high

pressure neurological syndrome. *Br. J. Pharmac.*, **76,** 447–452.

BICHARD, A.R., LITTLE, H.J. & PATON, W.D.M. (1981). The involvement of GABA in the high pressure neurological syndrome (HPNS). *Br. J. Pharmac.*, **74,** 221P.

BOWERY, N.G. & BROWN, D.A. (1974). Depolarising actions of γ-aminobutyric acid and related compounds on rat superior cervical ganglia *in vitro*. *Br. J. Pharmac.*, **50,** 205–218.

BRAUER, R.W., BEAVER, R.W., LAHSER, S., McCALL, R.D. & VENTERS, R. (1979). Comparative physiology of the high pressure neurological syndrome – compression rate effects. *J. appl. Physiol.*, **46,** 128–135.

BRAUER, R.W., MANSIFLED, W.M., BEAVER, R.W. & GILLEN, H.W. (1979). Stages in development of high pressure neurological syndrome in the mouse. *J. appl. Physiol.*, **46,** 756–765.

BROWN, D.A. & GALVAN, M. (1977). The influence of neurological transport on the action of γ-aminobutyric acid on mammalian ganglion cells. *Br. J. Pharmac.*, **59,** 373–378.

BROWN, D.A. & MARSH, S. (1974). A very simple method for recording ganglion depolarisation. *J. Physiol.*, **246,** 24–26P.

CAMPENOT, R.B. (1975). The effects of high hydrostatic pressure on transmission at the crustacean neuromuscular junction. *Comp. Biochem. Physio.*, **52B,** 133–140.

COHEN, M.L., CHAN, S.-L., WAY, W.L. & TREVOR, A.J. (1973). Distribution in the brain and metabolism of ketamine in the rat after intravenous administration. *Anesthesiology*, **39,** 370–376.

COHEN, M.L. & TREVOR, A.J. (1974). On the cerebral accumulation of ketamine and the relationship between the metabolism of the drug and its pharmacological effects. *J. Pharmac. exp. Ther.*, **189,** 351–358.

GREEN, C.J., HALSEY, M.J. & WARDLEY-SMITH, B. (1977). Possible protection against some of the physiological effects of high pressure. *J. Physiol.*, **267,** 47P.

HALSEY, M.J. & WARDLEY-SMITH, B. (1975). Pressure reversal of narcosis produced by anaesthetics, narcotics and tranquillisers. *Nature*, **257,** 811–813.

HALSEY, M.J., WARDLEY-SMITH, B. & GREEN, C.J. (1978). Pressure reversal of general anaesthesia – a multi-site expansion hypothesis. *Br. J. Anaesth.*, **50,** 1091–1096.

HENDERSON, J.V. & GILBERT, D.L. (1975). Slowing of ionic currents in the voltage clamped squid axon by helium pressure. *Nature*, **258,** 351–352.

HENDERSON, J.V., LOWENHAUPT, M.T. & GILBERT, D.L. (1977). Helium pressure alteration of function in squid giant synapse. *Undersea Biomed. Res.*, **4,** 19–26.

HILLS, G.J. (1969). Pressure coefficients of electrode processes. In: *Advances in High Pressure Research 2*. ed. Bradley, R.S. pp. 225–255. Academic Press: New York.

HUANG, L.-Y.M. & BARKER, J.L. (1980). Pentobarbitone: stereospecific actions of (+) and (−) isomers revealed on cultured mammalian neurones. *Science*, **207,** 195–197.

KENDIG, J.J., SCHNEIDER, J.M. & COHEN, E.N. (1978). Pressure, temperature and repetitive impulse generation in crustacean axons. *J. appl. Physiol.*, **45,** 742–746.

KENDIG, J.J., TRUDELL, J.R. & COHEN, E.N. (1975). Effects of pressure and anaesthetics on conduction and synaptic transmission. *J. Pharmac. exp. Ther.*, **195,** 216–224.

KOBLIN, D.D., LITTLE, H.J., GREEN, A.R., DANIELS, S., SMITH, E.B. & PATON, W.D.M. (1980). Brain monoamines and the high pressure neurological syndrome. *Neuropharmac.*, **19,** 1031–1038.

LEVER, M.J., MILLER, K.W., PATON, W.D.M. & SMITH, E.B. (1971). Pressure reversal of anaesthesia. *Nature*, **231,** 368–371.

MILLER, K.W. (1977). The opposing physiological effects of high pressures and inert gases. *Fedn. Proc.*, **36,** 1663–1667.

MILLER, K.W., PATON, W.D.M., SMITH, R.A. & SMITH, E.B. (1973). The pressure reversal of anaesthesia and the critical volume hypothesis. *Mol. Pharmac.*, **9,** 131–143.

MILLER, K.W. & WILSON, M.W. (1978). The pressure reversal of a variety of anaesthetic agents in mice. *Anesthesiology*, **48,** 104–110.

MILLER, K.W., WILSON, M.W. & SMITH, R.A. (1978). Pressure resolves two sites of action for inert gases. *Mol. Pharmac.*, **14,** 950–959.

NICOLL, R.A. (1977). The effects of anaesthetics on synaptic excitation and inhibition in the olfactory bulb. *J. Physiol.*, **223,** 803–814.

SCHOLFIELD, C.N. (1980). Potentiation of inhibition by general anaesthetics in neurones of the olfactory cortex *in vitro*. *Pflugers Arch.*, **383,** 249–255.

SMITH, R.A., SMITH, M., EGER, E.I., HALSEY, M.J. & WINTER, P.M. (1979). Nonlinear antagonism of anaesthesia in mice by pressure. *Anaesth. Analg.*, **58,** 19–22.

TRUDELL, J.R. (1977). A unitary theory of anaesthesia based on lateral phase separations in nerve membranes. *Anesthesiology*, **46,** 5–10.

WANN, K.T., HARPER, A.A., WILCOCK, S.E. & MACDONALD, A.G. (1977). Excitatory and inhibitory effects of pressure on neuronal membranes. *Med. Subaqua. Hyperbare.*, **16,** 284–286.

WANN, K.T. & MACDONALD, A.G. (1980). The effects of pressure on excitable cells. *Comp. Biochem. Physiol.*, **66A,** 1–12.

WINTER, P.M., SMITH, R.A., SMITH, M. & EGER, E.I. (1976). Pressure antagonism of barbiturate anesthesia. *Anesthesiology*, **44,** 416–419.

WOOD, J.D. & HERTZ, L. (1980). Ketamine-induced changes in the GABA system of mouse brain. *Neuropharmac.*, **19,** 805–808.

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