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THE EFFECT OF ANAESTHETIC AGENTS ON CEREBRAL CORTICAL RESPONSES IN THE RAT

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1 In rats, surgically anaesthetized with Urethane, an increase in the depth of anaesthesia upon administration of ethyl carbamate (Urethane), pentobarbitone sodium (Nembutal), thiopentone sodium (Intraval), althesin, ketamine, trichloroethylene, halothane, methoxyflurane, diethyl ether, ethyl-vinyl ether, cyclopropane, enflurane or chloroform resulted in a dose-dependent increase in the latency, and decrease in the amplitudes of the initial positive and negative components of the short latency cortical response to electrical stimuli applied to the forepaw.

2 The same changes were seen when starting from initially unanaesthetized rats and anaesthetizing them with Urethane.

3 With all the inhalational agents used these changes lasted for as long as the administration except with nitrous oxide where the changes in the cortical response were transient.

4 The tranquillizing agents diazepam, chlordiazepoxide, and haloperidol showed no such action. Chloral hydrate and chlorpromazine, on the other hand, produced moderate changes in the evoked cortical response similar to those seen with the other anaesthetic agents used.

Introduction

A wide range of chemical agents showing an equally wide range of chemical structures can produce general anaesthesia under pertinent conditions. Two generalizations can be made for these chemicals. First their anaesthetic potency correlates with their lipid solubility. This observation first proposed by Meyer (1899) and Overton (1901) has been repeatedly confirmed and extended (see e.g. Miller, Paton, Smith & Smith, 1973; Franks & Lieb, 1978). Secondly, their effects can be reversed by increasing the ambient barometric pressure with helium, for terrestrial animals, or increasing the ambient hydrostatic pressure, for aquatic animals in a variety of species (see e.g. Lever, Miller, Paton & Smith, 1971; Halsey & Wardley-Smith, 1975).

Because of the consistency of pressure reversal of anaesthesia this may be used as a tool to judge whether a particular effect of anaesthetics in a model system is relevant to its production of anaesthesia in the whole animal (Little & Paton, 1979). It has been shown that the effect of ethyl carbamate (Urethane) on the cerebral cortical response is pressure reversible (Angel, Gratton, Halsey & Wardley-Smith, 1980). Thus the effect upon the cerebral cortical response of this particular anaesthetic might be a specific correlate of its anaesthetic, as opposed to other effects. The following series of experiments to investigate the effect of a wide variety of anaesthetic agents upon the cerebral response to stimulation of the periphery has been undertaken to see whether other anaesthetic agents produce the same effect upon the cortical evoked response as that seen with Urethane.

Methods

One hundred and twenty female albino rats (Sheffield Strain) in the weight range 190–210 g were used in this study. Two types of experiment were performed either in the acute or chronic preparation.

Acute experiments

A total of 108 animals were anaesthetized with ethyl carbamate (Urethane) administered intraperitoneally as a 25% solution in saline at a dose of 1.25 g/kg (i.e. a dose that prevents visible reflex responses to surgery). The animal then underwent a tracheal cannulation, a mid-line skin incision over the cranium, opening of the foramen magnum (to prevent cerebral oedema see Angel, Berridge & Unwin 1973), and an extensive craniotomy to expose the left cerebral hemisphere from which the dura mater was reflected. The animals were then mounted in a stereotaxic frame and a pool constructed over the cerebral cortex by gripping the cut skin edges between an inner perspex ring and an outer metal clip. This pool was then filled with liquid paraffin (B.P.) at 37°C which had been saturated with saline to remove any organic

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Chronic experiments

Twelve animals were used for these experiments. Under thiopentone sodium/trichloroethylene anaesthesia and with full aseptic precautions, three small (10BA) screws were implanted into the skull; one over the sensory cortical area for the forepaw, the second some 4 mm caudad to serve as an indifferent electrode and the third on the opposite side of the skull to act as an earth electrode. These screws were then wired into a miniature socket and the whole assembly embedded, together with the cut skin edges, in cold-curing acrylic cement (Simplex Rapid, Dental Fillings Ltd).

For recording, the animal was treated with chlordiazepoxide (15 mg/kg: see below) and suspended in a hammock.

Recording techniques

Responses from the cerebral cortex, via fine silver wires in the acute preparation and from the epidural screws in the chronic preparation, were amplified with resistance-capacity coupled amplifiers and displayed on a cathode ray oscilloscope or averaged with a special purpose digital computer (Biomac 1000, Data Labs Ltd) the output from which was fed into a PDP 11/10 Computer (D.E.C. Ltd) for subsequent statistical evaluation.

Stimulation

Electrical stimulation was accomplished by wrapping gauze strips, soaked in 3 M NaCl, one around the wrist (negative) the other around the two middle digits (positive). These were connected to an isolated stimulator which provided pulses of up to 100 V in amplitude with a duration of 50 μs. Supramaximal stimuli for the cortical response were used throughout each experiment.

Care was taken when applying the gauze strips not to occlude the circulation to the forepaw.

Administration of drugs

Anaesthetic vapours and gases were given in an oxygen stream, saturated with water vapour, and delivered to one arm of a T-piece with the animal's tracheal cannula inserted into the base of the T. The other arm of the T-piece was connected to an anaesthetic venting system.

All water soluble drugs were administered in solution in saline at 37°C via a tail vein, except for ethyl carbamate which was administered intraperitoneally.

Of the gaseous and vapourizable anaesthetics cyclopropane and nitrous oxide inspired concentrations were determined by measuring their gas flow relative to that of the oxygen flow; di-ethyl ether, enflurane, halothane, methoxyflurane and trichloroethylene were delivered from calibrated vapourizers (Cyprane Ltd). The other vapours were crudely administered by diverting a measured portion of the oxygen flow through a Dreschel bottle containing the anaesthetic.

Results

Three series of experiments were performed

In the first the animals were initially anaesthetized with Urethane at a dose of 1.25 g/kg and subsequently given incremental doses of various anaesthetic agents.

In the second, animals with electrodes implanted over the short latency receiving area for the forepaw were studied, initially unanaesthetized, and subsequently given incremental doses of Urethane to very deep levels of anaesthesia.

In order to minimize the effects of extraneous variables such as handling and restraint upon the evoked responses in these initially unanaesthetized animals it became necessary to devise a technique for minimizing this stress. To this end a third series of experiments was performed in which the animals were initially anaesthetized with Urethane (1.25 g/kg) and the effects of various tranquillizers upon the evoked cortical response to forepaw stimulation were assessed.

Quantification of the evoked cortical response

In animals surgically anaesthetized with Urethane (1.25 g/kg) the early part of the evoked cortical response can best be described as a wave of surface positivity interrupted by one or two early prominent negative components, thus forming a complex waveform which can be split into initial positive (Pi, initial negative (Ni), second positive (Ps) and second negative waves (Ns) respectively (see Figure 2b). In the unanaesthetized animal the evoked cortical response was predominantly negative going, showing definite Pi, Ni, and Ns waves but with the second positive wave seen only as a small inflection between Ni and Ns (see Figure 2b compare traces (i) and (iv)). Occasionally the initial negative wave shows a separation, itself, into two components (see Figure 2b). The presence of a large negative wave in the cortical response apparently cuts short the initial positive wave of the response (see Figure 2b compare traces (u) and (s)). Since the effect of Urethane is to increase the latency of the response and decrease the amplitude of the initial positive wave when going from surgical to deeper levels of anaesthesia (see

Figure 2b, compare traces (s) and (d)) the two measures of latency (L) and Pi amplitude were combined into a single response parameter namely $1/L \times Pi$. Thus for all observations where the starting level of anaesthesia was 1.25 g/kg Urethane this is the response parameter given.

In the condition where the starting level was the unanaesthetized state the combination of these two measures would be clearly misleading (see above). Thus here the measure of the evoked responses is expressed as the size of the initial negative wave (measured from the peak of Pi to the trough of Ni) times the reciprocal of the latency.

Effect of tranquillizers

For this series of experiments 19 animals were used to which a variety of drugs over the hypnotic, sedative and tranquillizer spectrum were administered. Six animals were given chloral hydrate (up to 100 mg/kg), 5 chlorpromazine (up to 35 mg/kg), 4 haloperidol (up to 10 mg/kg), 2 chlordiazepoxide (up to 30 mg/kg), and 2 diazepam (up to 50 mg/kg) i.e. to fatal or near fatal levels. For haloperidol, chlordiazepoxide and diazepam no statistically significant difference was seen between the evoked responses at the start and after the administration of these drugs. For chloral hydrate the evoked cerebral responses showed statistically significant (Student's t test, $P<0.005$, 2 tailed) changes in latency and Pi amplitude at doses of 70+ mg/kg and at doses of 25+ mg/kg for chlorpromazine. The results for this series of experiments are shown graphically in Figure 1.

Effect of anaesthetic agents

Ethyl carbamate The effect of this anaesthetic agent on the evoked response, in rats pretreated with chlordiazepoxide 15 mg/kg, was to give a steady decrease in the size of the initial negative wave of the cortical response and an increase in the latency of the response when taken from the unanaesthetized to the deeply anaesthetized state. For example the latency to the start of the response increased from 3.50 ± 0.08 (s.e.mean, $n=9$) ms in unanaesthetized animals to 4.20 ± 0.05 ($n=86$) at the usual starting level of anaesthesia of 20.51 mM, a highly statistically significant increase ($P<0.001$), and at the same time the initial negative wave of the cortical response was approximately halved (see Figure 2).

For comparison of the effects of the various anaesthetics the doses administered have all been expressed as mmol/l body water, taking the average total body water of female rats to be 650 ml/kg body weight (see Spector, 1956) and assuming a uniform distribution of the anaesthetic molecule in this aqueous phase.

Another way of showing the lack of effect of chlordiazepoxide is also illustrated in Figure 4a in which the hatched area includes the mean ± s.e.mean of the initial negative wave from 12 animals with a starting level of 20.51 mM Urethane without chlordiazepoxide.

Other intravenous agents All the other intravenous agents were used superimposed upon a basal level of Urethane anaesthesia. This procedure was adopted for 2 main reasons: (a) The amplitude of the evoked cerebral response was much larger when recorded from the surface of the cortex directly rather than with the electrode resting on the dura as in the implanted electrode experiments, e.g. at basal levels

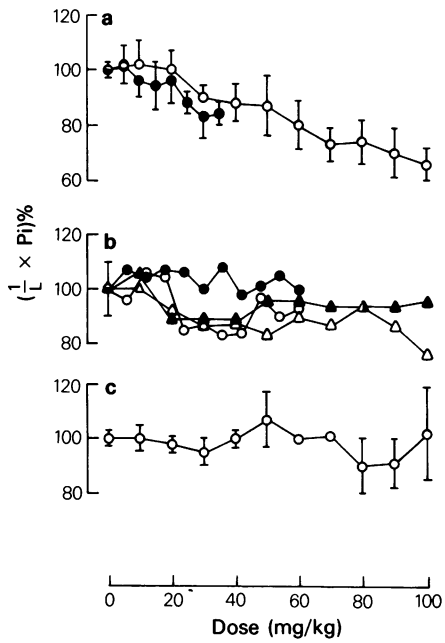

Figure 1 The effect on the evoked cortical response in animals anaesthetized with Urethane of: (a) The hypnotic, chloral hydrate ($n=6$, ○) and the tranquillizer, chlorpromazine ($n=6$, ●). Each point is the mean change in the average cortical response expressed as a percentage of the starting level and the vertical lines indicate s.e.mean. (b) The minor tranquillizers diazepam ($n=2$, filled symbols) and chlordiazepoxide ($n=2$ open symbols). Each point on the graph represents the mean change in the cortical response for each animal and the vertical lines indicate the absolute scatter in the mean starting responses. (c) The major tranquillizer haloperidol ($n=10$). Each point represents the mean change in evoked response and the vertical lines show s.e.mean. The ordinates show the cortical response as a percentage of the starting value of $Pi \times 1/L$. The abscissae show the dose of drug used as mg/kg (× 1 (a); × 2 (b); × 10 (c)).

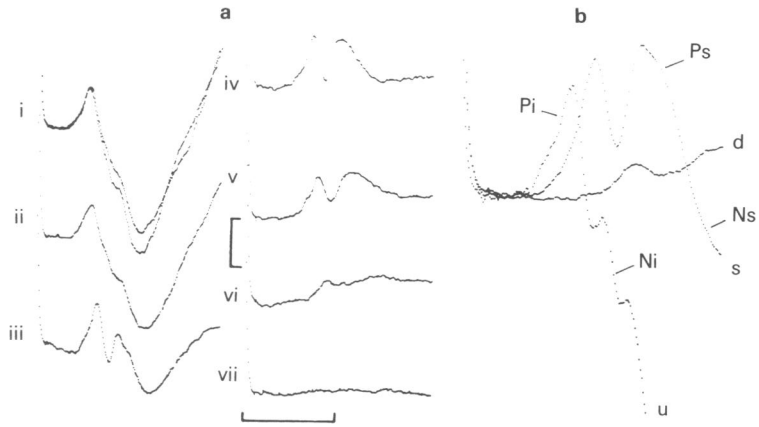

Figure 2 The effect of Urethane on the average cerebral evoked response. Each average is to 120 consecutive stimuli delivered to the right forepaw at a rate of 1/s. The animal was initially unanaesthetized but given the tranquillizer chlordiazepoxide (15 mg/kg). (a) (i) Shows two averaged evoked cerebral responses superimposed in the unanaesthetized animal and single averages taken 3 min after the following doses of urethane administered intraperitoneally: (ii) 0.5 g/kg; (iii) 1.0 g/kg; (iv) 1.25 g/kg; (v) 1.5 g/kg; (vi) 2.0 g/kg and (vii) 2.5 g/kg. (b) A series of records, taken from another animal, superimposed to emphasize the differences in latencies and conformation of the responses in the unanaesthetized (u), the surgically anaesthetized (s 1.25 g/kg Urethane) and the deeply anaesthetized (d) 2.5 g/kg Urethane) animal. The major components of the evoked cortical responses are also indicated. Pi: initial positive, Ni: initial negative, Ps: second positive and Ns: second negative waves respectively. The horizontal calibration represents 10 ms for (a) and 5 ms for (b). The vertical calibration 20 μV for (a) and 10 μV for (b).

of Urethane anaesthesia the initial positive wave was $222.2\,\mu V \pm 6.2$ ($n = 54$) from the cortex and $32.5\,\mu V \pm 4.3$ ($n = 12$) via the dura. However, in the direct recording experiments the position of the active electrode had to be more precise and the best point i.e. where Pi × 1/L was largest had to be found by trial and error, by searching a small grid between 3–4 mm lateral and 0–1 mm anterior to the Bregma, at the start of the experiment. (b) Urethane is very slowly metabolized, so that the other anaesthetic agents could be superimposed upon a stable basal level without any interference to the cortical responses, from levels of 'attention' or 'sleep' as found in the unanaesthetized preparation (Angel, 1967). All the experiments could, in fact, be completed within 90 min. Over this time span no statistically significant changes could be detected in the initial components of the cortical responses (see Angel *et al.*, 1980).

All the intravenous agents tested showed the same effect as Urethane i.e. an increase in latency and decrease in amplitudes of the initial positive and negative waves of the cortical response as the anaesthetic level was increased (see Figure 3a). The dose-response curves for the anaesthetics are plotted in Figure 4. A direct comparison of their anaesthetic activity was, therefore, possible in terms of the concentration required to reduce the evoked potential to 50% of its starting level. These were, in order of potency: althesin (0.046 mM), thiopentone (0.055 mM), ketamine (0.144 mM), pentobarbitone (0.297 mM) and Urethane (5.33 mM).

Inhalational agents Again all the inhalational agents tested showed the same effect on the evoked cortical response as Urethane i.e. a dose-dependent increase in latency and decrease in the early components of the cortical response. Figure 3 shows the effect of inhalation of cyclopropane and halothane. Each record is the average of 60 consecutive responses at various times before, during and after the administration of the anaesthetic, showing both its effect on the cortical response and the complete reversibility of the changes seen in the evoked response upon its withdrawal. This figure also illustrates the stability of the basal level of anaesthesia obtained with Urethane since the records were obtained from the same animal over a time span of 80 min.

The quantitative effects of the various inhalational anaesthetic agents are shown in Figure 4 (c) and (d), in which the effect of the anaesthetics after the cortical response had reached a steady state is plotted against the inspired concentration. Qualitatively similar results were obtained with ethyl-vinyl ether and chloroform.

Although nitrous oxide showed the same effect on the evoked cortical responses as all the other anaesthetic agents used its effect was always found to

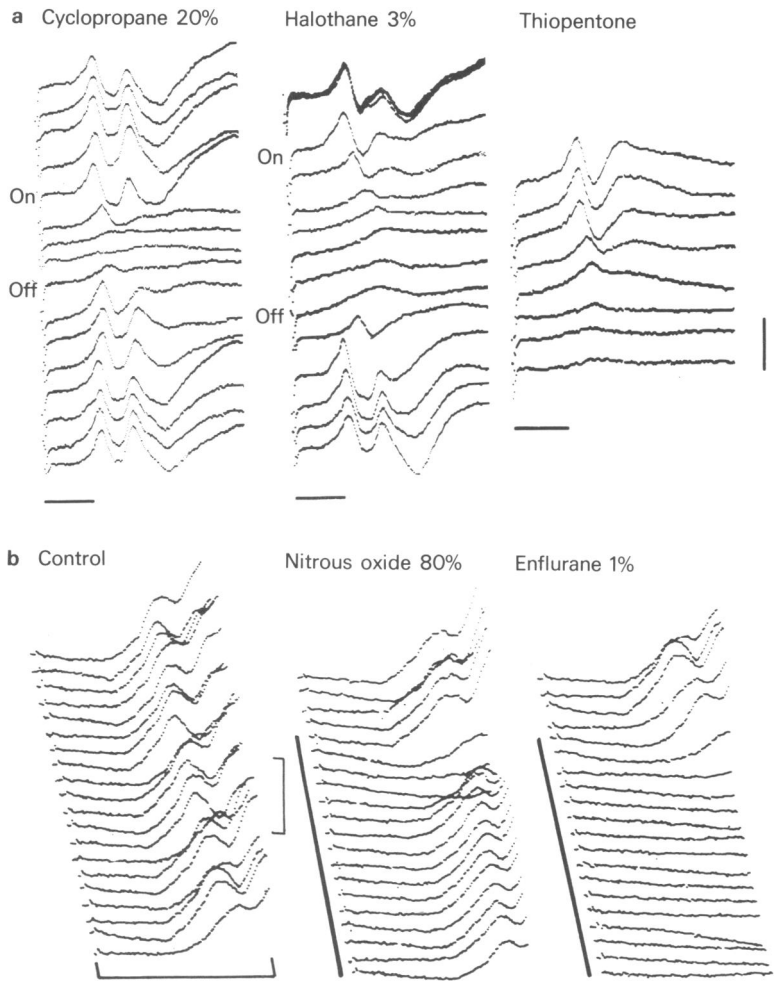

Figure 3 (a) The effect of various anaesthetics on the averaged evoked cortical responses ($n = 60$ at a rate of 1/s) to supramaximal electrical stimulation of the forepaw in animals anaesthetized with Urethane (1.25 g/kg). The averages were taken every min before and during the administration of cyclopropane (20%) and halothane (3%) and every 2 min after the anaesthetic was turned off. The beginning and cessation of the anaesthetic administration is indicated by 'on' and 'off' respectively. In the case of halothane the first 4 averages have been superimposed to indicate the stability of the starting responses. Both these anaesthetics were administered to the same animal with a period of 1 h between the two anaesthetics. The right hand column shows the effect of thiopentone sodium in another animal. The top record shows the starting level and each subsequent trace was taken after the administration of incremental doses of 12.5 mg/kg. The horizontal lines represent a time calibration of 5 ms and vertical line a voltage calibration of 300 μV. (b) A series of records, from one animal, showing the transience of the effect of nitrous oxide (80%) compared to another inhalational anaesthetic (enflurane 1%). Each series of records shows the averages to 60 consecutive supramaximal electrical stimuli applied to the forepaw at a rate of 1/s in an animal with a basal anaesthetic level of 1.25 g/kg of Urethane with the averages obtained every min for a 20 min recording period. The left hand column of responses shows the variation of the cortical evoked responses in this animal over the same time span. The onset and continued administration of the anaesthetic is indicated by the thick line to the right of the records. There was a time delay of 1 h between the administration of the two anaesthetics. The horizontal bar represents a time calibration of 10 ms and the vertical one a voltage calibration of 200 μV.

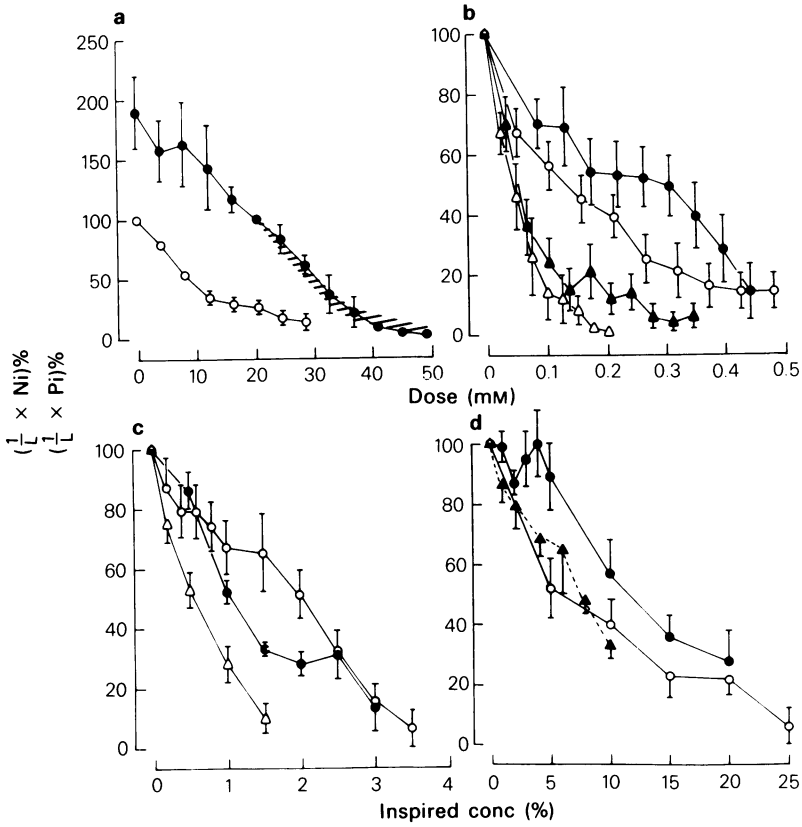

Figure 4 The quantitative effects of the various anaesthetics used in this study. Each point on the graphs represents the mean decrease in the average cortical response in a number of experiments with 100% representing the mean response in animals anaesthetized with 1.25 g/kg Urethane. The vertical bars represent s.e.mean. (a) The effect of Urethane on the evoked cortical response in 4 animals taken from the unanaesthetized (treated with 15 mg/kg chlordiazepoxide) to the deeply anaesthetized state (●); the ordinate scale represents the % change in (1/L × Ni). The shading represents the envelope of the curve of (1/L × Ni)% from 12 animals initially anaesthetized with Urethane (1.25 g/kg) without chlordiazepoxide. The effect of Urethane on the average cortical responses in 12 animals initially anaesthetized with 1.25 g/kg Urethane (○); the ordinate scale in this case (and for all the other graphs represents the % change in (1/L × Pi). (b) The effects of adding althesin (△, $n = 5$), intraval ▲, $n = 5$), ketamine (○, $n = 7$) and nembutal (●, $n = 8$) to animals initially anaesthetized with Urethane (1.25 g/kg). The abscissae for (a) and (b) show the dose of added anaesthetic as mmol/kg body water (see text). (c) The effect of methoxyflurane (△, $n = 12$), halothane (●, $n = 6$) and enflurane (○, $n = 5$). The abscissa scale shows the inspired % concentration of the anaesthetic vapour. (d) The effect of cyclopropane (○, $n = 9$), ether (▲, $n = 6$) and trichloroethylene (●, $n = 9$). The abscissa scale shows the % inspired concentration × 10 for trichloroethylene and × 1 for cyclopropane and ether.

be transient. Unlike the other inhalational agents whose effect lasted for as long as they were administered that of nitrous oxide quickly wore off with the cortical response returning to pre-administration levels within 18.9 min ± 2.35 ($n = 15$).

This effect is shown in Figure 3b in which the effect of nitrous oxide is contrasted with that of enflurane.

Expressing the concentration of the inhalational anaesthetics as that percentage inspired concentration needed to reduce the cortical response to 50% of its starting level allows a comparison of their potencies. These were, in ascending order, methoxyflurane (0.55 ± 0.19, $n = 12$), halothane (1.05 ± 0.1, $n = 6$), trichloroethylene (1.17 ± 0.29, $n = 9$), enflurane (2.0 ± 0.19, $n = 5$), ether (5.1 ± 0.4, $n = 6$) and cyclopropane (5.5 ± 0.22, $n = 6$).

Conversion of these inspired concentrations to concentrations in the aqueous phase using the formula: Caq = Pc/RT (where P = partial pressure; c = water: gas partition coefficient; T = absolute

temperature and R the international gas constant) gives a differing order of potencies namely: halothane (0.33 mM), cyclopropane (0.52 mM), enflurane (0.63 mM), trichloroethylene (0.78 mM), methoxyflurane (0.97 mM) and ether (5.11 mM).

Discussion

Previous investigations into the effects of anaesthetic agents upon the cerebral response to peripheral stimulation have been inconclusive; some authors (Derbyshire, Rempel Forbes & Lambert, 1936; French, Verzeano & Magoun, 1953; Lader & Norris, 1968) reported little or no effect whilst others (Brazier, 1953; Dawson, Podachin & Schatz, 1963; Domino, Corsen & Sweet, 1963; Angel, 1967; Angel *et al.*, 1973; Angel *et al.*, 1980), showed a definite alteration of the cerebral evoked response in a variety of animal species including man. The present investigation shows that all of the commonly used anaesthetic agents, which were tested, produced a consistent alteration in the cerebral evoked response to forepaw stimulation. This was to give a dose-dependent increase in the latency of the response and a decrease in the amplitudes of the initial components of the response. However, this common observation was seen in animals already anaesthetized with ethyl carbamate and the effects of the other anaesthetic agents superimposed upon this basal anaesthetic. The experiments reported here upon the effect of ethyl carbamate in the initially unanaesthetized rat with implanted electrodes show that for this anaesthetic there is a response continuum relating the magnitude and latency of the cerebral evoked response to anaesthetic dose. Since this effect had already been reported in the rabbit with electrodes implanted over the somatosensory cortical receiving area to electrical stimulation of the forepaw for trichloroethylene alone, pentobarbitone alone as well as to ethyl carbamate alone (Angel *et al.*, 1973) it is unlikely that the common effect seen under the circumstances of the present experiments could be an artifact of the technique of superimposing different anaesthetic agents upon an ethyl carbamate base. The only effect of ethyl carbamate which is likely to distort the results seen in the present investigation is its ability to reduce presynaptic inhibition (Schmidt, 1971) which might make some anaesthetics, e.g. the barbiturates, less potent than would normally be the case.

The observation that the changes seen with ethyl carbamate are pressure reversible (Angel *et al.*, 1980) as are those with althesin, halothane and nitrous oxide (Angel, Halsey & Wardley-Smith, unpublished observations) and the behavioural reversal of anaesthesia at high pressure seen with a variety of anaesthetic agents (Johnson & Flager, 1950; Lever *et al.*, 1971; Halsey, Eger, Kent & Warne, 1975; Miller, 1975), coupled with the present demonstration of the common effect of agents used clinically for the production of general anaesthesia would seem to indicate that this common effect may be related to anaesthesia *per se*. If this is so then one would expect that the ability of an anaesthetic agent to alter the cerebral evoked response should also correlate with its lipid solubility in accordance with the Meyer-Overton rule. The membrane: buffer coefficients for the various anaesthetics have been plotted against their ED_{50}s in Figure 5 which shows that there is a reasonable agreement between lipid solubility and anaesthetic potency. Statistical analysis of the regression gives a coefficient of linear regression of -0.92 which is statistically highly significant ($P < 0.001$).

Of the inhalational anaesthetic agents studied, only one was found whose effect did not last for as long as it was administered. Nitrous oxide always gave a transient change in the cortical evoked response which lasted, on average, for 19 min (range from 12–50 min) with inspired concentrations from 60–80%. A similar, though more prolonged, action has been reported in the cat. In this animal 75% nitrous oxide initially gives hypersynchronous elec-

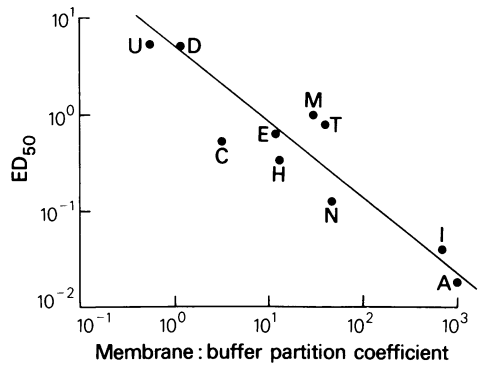

Figure 5 This shows the ED_{50} for the anaesthetic agents (mmol/l body water ordinate) plotted against their membrane: buffer partition coefficients. The membrane:buffer coefficients for althesin (A) and pentobarbitone sodium (N) have been taken from Richards & White (1981), those for Urethane (U), halothane (H), trichloroethylene (T), cyclopropane (C), di-ethyl ether (D) and methoxyflurane (M) are from Seeman (1972) and those for enflurane (E) and thiopentone sodium (I) have been estimated from Figure 5 of Seeman (1972). The ED_{50}s for some anaesthetics were corrected for protein binding assuming 70% for thiopentone (Davis, 1975), 40% for pentobarbitone (Dundee, 1974) and 40% for althesin (Child, Gibson, Harnby & Hart, 1972). The line drawn through the points is the calculated regression line where $\log(ED_{50}) = -0.699 \times \log$ (membrane:buffer partition coefficient) $+0.546$.

troencephalographic activity which changes to the normal waking-sleeping pattern after 2–3 h with no remnant of the hypersynchronous pattern being seen after 4–5 h (Mori & Winters, 1975). This transient effect of nitrous oxide, at sub-anaesthetic concentrations, is not seen at hyperbaric pressures obtained with helium with a partial pressure of nitrous oxide of 1.4 ATA (Angel, Halsey & Wardley-Smith, unpublished observations). The mechanism by which this transient effect is produced at sub-anaesthetic concentrations and normobaric pressure is unknown and requires a more complete investigation.

Under the conditions of the present experiments the tranquillizers chlordiazepoxide, diazepam and haloperidol gave no change in the cerebral response evoked by peripheral stimulation; whilst the major tranquillizer chlorpromazine and the hypnotic chloral hydrate gave small (20% maximum) but statistically significant changes at doses of 0.12 mmol/l body water and 0.63 mmol/l respectively. However, all of these drugs can produce in the rat a state resembling, behaviourally, anaesthesia. This is obviously achieved in a different way from that produced by general anaesthetic agents. Chlorpromazine potentiates the action of other anaesthetic agents and it could be this potentiation effect on the basal ethyl carbamate anaesthesia which gave the observed changes in the cerebral evoked responses. An alternative, but less likely explanation, is that chlorpromazine has been shown to block frog sciatic nerve conduction at 22°C at a dose of 10 μmol/l (Seeman, 1972). The minimum dose for an effect in the present series of experiments was 0.12 mmol/l which could have given some degree of nerve block at the higher temperature of 37°C. The action of chloral hydrate on the other hand could have been due to its conversion to trichloroethanol and that its effect was due to the small quantities of this chemical which gave the observed effect on the cerebral evoked responses. However, the major observation remains that some potent tranquillizers do not alter the cerebral evoked response. This observation allows a possible classification of chemicals which produce 'anaesthesia' into those compounds which disallow, in some manner, the access of afferent information to the cerebral cortex and those which do allow the information to reach the cerebral cortex but uncouple the arrival of the message from the processes which lead to its subsequent interpretation, in an entirely different manner.

Finally the common effect of all the general anaesthetic agents used i.e to increase the latency of the cortical response to peripheral stimulation and to decrease its amplitude can be achieved by several mechanisms. The two simplest are (a) that the responsiveness of the cortex itself is decreased by anaesthetic chemicals or (b) the sensory message is attenuated somewhere along the afferent pathway to the cerebral cortex or additionally, a combination of these two. The evidence so far (see Angel, 1977; 1980) suggests that the second of the above alternatives is the most likely.

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