THE EFFECT OF ANAESTHETIC AGENTS ON PRIMARY CORTICAL EVOKED RESPONSES

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SUMMARY

(1) The effect of increasing dosage of ethyl carbamate (urethane), trichloroethylene and pentobarbitone anaesthesia is to decrease the amplitude, increase the latency and produce a more stereotyped response, recorded from the short latency receiving area of the cerebral cortex to electrical or mechanical limb stimulation in both chronic and acute animals. (2) The extent of the short latency receiving area (defined as that from which responses with the shortest latency + 12.5% of this latency could be obtained) increased in extent from the lightly to the deeply anaesthetized state. (3) The only consistent non-nervous change produced by these anaesthetic agents was a decrease in arterial PO₂ as the anaesthetic depth was increased. (4) That cerebral hypoxia was not the cause of the changes seen in the evoked response was shown by the fact that the effect of the anaesthetic agents was the same in animals respiring 95% O₂, 5% CO₂ or in animals artificially respired. (5) It is concluded that the anaesthetic agents exert their effects on a central nervous structure. (6) Animals with cerebral oedema appear to be anaesthetic resistant. No change in the evoked cortical response was seen in any animal which showed the slightest signs of cerebral oedema.

Most research on the effects of general anaesthetic agents on the central nervous system has been concentrated on the responses of the fourth order sensory neurones (in the sensorimotor cortex) to peripheral stimuli. The responses recorded from the cortical surface by peripheral stimulation were found to be unaffected by pentobarbitone (Derbyshire et al., 1936; French, Verzeano and Magoun, 1953) or decreased in amplitude and increased in latency with pentobarbitone (Brazier, 1953) or trichloroethylene (Dawson, Podachin and Schatz, 1963). These latter findings were confirmed by Angel (1967b) in rabbits with electrodes implanted over the sensorimotor cortex when the animals were taken from the awake to the deeply anaesthetized state with pentobarbitone, trichloroethylene or ethyl carbamate. Decreased cortical responses in man have been reported by Domino, Corssen and Sweet (1963) for sodium thiamicynl, nitrous oxide, diethyl ether and cyclopropane. However, Lader and Norris (1968) using nitrous oxide and Abrahamian and associates (1963) using thiopentone found no change in the human evoked cortical response.

Thus little agreement has been reached on the effects of general anaesthetic agents on the central nervous system. The experiments to be reported in this paper are on the effects of anaesthetic agents on the cerebral evoked responses in both acute and chronic preparations and have been reported, in brief, elsewhere (Angel, 1967b; Angel and Unwin, 1969).

METHODS

(i) Chronic experiments.

Experiments were performed on six rabbits. Using full aseptic precautions, brass screws were implanted over the primary cortical receiving area for the hind leg. The screws were inserted into the bone until their tips just touched the dura mater. The screws were connected by wires to a plug which was secured in place on the cranium with acrylic dental cement. After a recovery period of 7 days the animals were used to record cortical evoked responses. In two animals a plastic trough containing an electrode array to record the activity at the periphery was implanted and secured around the sciatic nerve; wires from this trough were led subcutaneously to the cranial plug. For the experiments the animal was suspended face
ANAESTHETIC AGENTS AND PRIMARY CORTICAL EVOKED RESPONSES

The foramen magnum was opened to extensive unilateral craniotomy, usually on the left-hand side. The skin of the abdomen was locally anaesthetized with ethyl chloride first so that the animal did not feel entry of the syringe needle. Pentobarbitone was administered as a sterile solution. For the administration of trichloroethylene the animal was removed from the hammock and placed in an airtight box through which a mixture of trichloroethylene vapour in air (2.5%) was pumped to anaesthetize the animal quickly. The animal was removed from the box, replaced in the hammock, and trichloroethylene 1.5-2.2% was administered as its vapour in a 95% oxygen, 5% carbon dioxide gas mixture via a cone which covered the nose and mouth. After a period of 1–6 months the animal was used for a terminal experiment using urethane as the anaesthetic (administered as a 25% solution in physiological saline). The animals were then killed and the position of the recording electrodes noted. In all, 8 full experiments were carried out with pentobarbitone, 6 with trichloroethylene and 3 with ethyl carbamate.

(ii) Acute experiments.

410 female albino rats in the weight range 180–210 g were used. They were anaesthetized with ethyl carbamate 25% in 0.9% saline (w/v) (290 animals) or sodium pentobarbitone 25 mg/ml in 0.9% saline (60 animals) administered intraperitoneally. The anaesthetic depth was adjusted by trial and error until the animal would just not withdraw its hindleg to a strong pinch to obtain a fixed starting level of anaesthesia. To achieve this condition, 1.3–1.5 g/kg of urethane or 27–33 mg/kg of pentobarbitone were required.

The animal’s trachea was cannulated. In those experiments with trichloroethylene anaesthesia (60 animals) the tracheal cannula was connected to a T-piece and trichloroethylene vapour 1.5–2.2% in air passed past the cannula.

Access to the cerebral cortex was allowed by an extensive unilateral craniotomy, usually on the left-hand side. The foramen magnum was opened to release c.s.f. pressure and prevent cerebral oedema. If the cortex became oedematous at any stage of the experiment the results were discarded (see later).

The animal was mounted rigidly in a stereotaxic frame, the head being held by a plug in each external auditory meatus and by a bar under the hard palate behind the incisor teeth held in place by a screw clip over the nose. The hind end of the animal was held by a steel pin placed transversely deep to the attachment of the back muscles and the dorsal surface of the sacrum. The animal was stretched between the ear plugs and the steel pin with its body suspended in air. The head and body clamps were mounted on a pair of lathe slides fixed at right-angles to each other. Using these lathe slides the animal could be moved parallel to, or at right-angles to, its longitudinal axis in the horizontal plane. The position of these lathe slides could be measured with an accuracy of ±5 μ with Mercuer lathe gauges. These gauges were set to read zero when the tip of a microelectrode was vertically above the midpoint between the ear plugs. An additional lathe slide mounted vertically carried an electrode holder (either for a micro- or macro-electrode). The borders of the skin incision were clamped between an inner perspex ring and an outer metal clip to form a leakproof pool. This pool was filled with liquid paraffin BP (which had been equilibrated with physiological saline to remove toxic acids), at a temperature of 37°C. The body temperature of the animal was maintained by a copper radiator placed beneath the animal through which water at 39°C was circulated. The heating was regulated to maintain the rectal temperature at 37±0.5°C.

Anaesthetic.

In the acute experiments the dose of urethane or pentobarbitone in any animal was increased in steps by 0.125 g/kg or 6.3 mg/kg given intraperitoneally. The percentage of trichloroethylene administered to the animal was also changed in 0.2% steps by mixing two airstreams, one bubbled through the trichloroethylene container, the other a bypass. Initial experiments showed that after an incremental dose of anaesthetic the cortical response changed to a new steady state within 30–45 sec. Thus in all cases observations were made starting at 2 min after the increased dose.

Recording.

The electrodes used to record surface potentials were of silver wire insulated to the tip which had been fused into a small sphere. Two such electrodes were used, one mounted on the vertical electrode
holder and the other placed permanently on the occipital cortex. Potentials from these electrodes were amplified by resistance-capacity coupled amplifiers. The frequency response characteristics of the amplifiers are indicated by the calibration in figure 3(d) which corresponds to a sine wave response, into a fixed output resistance, flat from 50 Hz to 3 kHz falling by —5 dB at 10 Hz and —9 dB at 10 kHz. Alternatively the height of the response would be attenuated by 40% at 10 Hz and by 65% at 10 kHz.

The amplified responses were displayed on an oscilloscope. Records were obtained by photography of several responses superimposed on the same frame, by recording the responses on magnetic tape, or by obtaining an averaged response with a special purpose digital computer the output from which was either via punched paper tape for subsequent analysis or displayed using an X-Y plotter. Averaging involves the algebraic summation of successive responses so that any feature that occurs consistently in response to the stimulus is then increased in direct proportion to the number summed, whilst random fluctuations superimposed on the response tend to cancel.

Stimulating.

Electrical stimuli were applied to the periphery of the animal by means of lint pads soaked in 3M NaCl solution. The negative electrode of the pair was wrapped around the wrist or ankle and the positive one around a digit. The pressure under the electrodes was kept as low as possible, and the lint pads were kept moist throughout the experiment. The stimuli were rectangular pulses of 0.1 msec duration continuously variable from 0 to 90 V, isolated from earth. The timing of the stimuli was controlled from a digital timing unit.

Blood pressure.

Measurements were made from the cannulated carotid artery with a Statham blood pressure transducer fixed firmly at heart level in 6 rats. The output was displayed on a pen recorder; drift was periodically checked for by means of a fixed reference pressure. All cannulae were heparinized and the animal given an i.v. dose of 500 units of heparin (Evans Medical Ltd), to prevent coagulation.

Respiratory rate and tidal volume.

A home-made pneumotachograph, consisting of a piece of glass tracheal cannula with two side arms 1 cm apart, was used. The side arms were connected to a Statham low-pressure transducer and the output displayed on a single channel pen recorder. Tidal volume was measured by integration of the inspiratory phase. Measurements were made in 6 rats.

Blood-gas analysis.

The arterial Po, and Pco, was estimated by removing 0.1-ml blood samples from the carotid artery. These samples were collected in heparinized glass capillary tubes and were transferred immediately to the estimation chamber of a 113-S1 Instrumentation Laboratories blood pH and gas analyser. Analyses were made in 10 rats breathing spontaneously, 6 curarized and artificially ventilated, and 5 breathing a 95% oxygen, 5% carbon dioxide gas mixture, anaesthetized with urethane; and in 2 groups of 4 rats breathing spontaneously anaesthetized with sodium pentobarbitone or trichloroethylene.

RESULTS

The sensory receiving area.

In rats just sufficiently deeply anaesthetized to abolish reflex withdrawal of the hind leg, responses of short latency and large amplitude were only obtained from a small area of the contralateral cortex following stimulation of the forepaw. This area was found to be rectangular in shape, 1 x 2 mm in size, with its long axis oriented in the medio-lateral axis and sited rostral to the coronal suture (Angel, 1962, 1967a; Angel and Unwin, 1969). The orientation of this area was at variance with that described by Dawson and Holmes (1966) who found the short latency area to be an oval with its long axis in the rostro-caudal axis. An attempt was made, therefore, to determine the orientation more accurately as follows.

If we make the assumption that the response from the short latency area results from the synchronous activation of a population of neurones which can be considered as a single dipole with constant spatial orientation (see fig. 1), then Gaussian analysis can be employed to determine this orientation.

The potential moving away from the centre of the dipole varies inversely with the square of the distance moved:

\[ V = K(1/d^2) \]

where \( V \) = potential and \( d \) = distance.

The component of this in the caudal axis (Vc) is:

\[ V_c = K \cos \phi/x^2 \]  

(1)
\( x = \text{distance in caudal direction, and the component in the medial direction (Vm) is:} \)

\[ V_m = K \sin \frac{\phi}{y^2} \quad (2) \]

\( y = \text{distance in the medial direction.} \)

From (1) and (2)

\[ \tan \phi = \sin \phi / \cos \phi = V_m y^2 / V_c x^2 \]

Thus if graphs of the amplitude of the cortical response versus the reciprocal of the distance squared from the origin are constructed \( \phi \) can be estimated. In ten experiments values for \( \phi \) between 70 and 80° were obtained, i.e. the area is orientated with its long axis almost in the medio-lateral axis.

![Diagram of theoretical dipole with its orientation in two dimensions](image)

Eidelberg and Jenkins (1966) showed that the area of cortex from which responses to stimulation of the contralateral hand could be obtained in the monkey was decreased when the depth of anaesthesia was increased. Thus one possible explanation of the decrease in amplitude of the cortical response with increase in anaesthetic depth (Angel, 1967b) is as a consequence of a possible change in distance between the cortical locus of activity and electrode position. Consequently, experiments have been performed to test this possibility. The extent of the cortical receiving area has been investigated in 12 rats at two depths of urethane anaesthesia. For these experiments the mean cortical responses were obtained from each of 24–30 positions of the cortical recording electrode, arranged as a stereotaxically positioned grid with 1-mm spacing. The results from one such experiment are shown in figure 2, which shows latency of the cortical response (vertical axis) versus the position of the active cortical electrode represented as a hypometric grid. The area of shortest latency is seen as a trough with latency of response increasing sharply as the electrode is moved rostrally, caudally or medially, but less steeply laterally. Because of the curvature of the cortical surface, representation of position as a stereotaxic co-ordinate foreshortens actual surface movement in the mediolateral direction. This has been accounted for in figure 2c, which shows a reconstruction of the cerebral surface with the shortest latency area enclosed in a solid line. Figure 2b shows the results obtained at the deeper level of anaesthesia and it can be seen that although the latency of the response at each site was increased, the area...
of cortex from which the shortest latency responses were obtained had actually increased in size. This increase was seen predominantly in the rostro-caudal axis. Thus the short latency area was changed from a rectangular area of size 1×2 mm into a square of approximately 2 mm side (fig. 2c, dashed line).

The area of shortest latency cortical responses was found in subsequent experiments by its stereotaxic position relative to a fixed landmark—the intersection between the sagittal and coronal sutures. In all the acute experiments the electrode was placed 3–4 mm lateral and 1–2 mm rostral to this landmark.

Cerebral evoked responses and anaesthesia.

Acute experiments. The short latency response to contralateral forepaw stimulation appears as a positive wave lasting 20–25 msec which is usually interrupted by a negative wave or inflexion. The response can be described as consisting of an initial positive wave (P₁, fig. 3b) followed by a first negative wave or inflexion (N₁, fig. 3b) which may be followed by a further positive wave (P₂, fig. 3b). Occasionally this second positive wave is replaced by a second negative wave (N₂, fig. 3c) especially when the animal is relatively "lightly" anaesthetized, i.e. reflex withdrawal only just abolished.

Measurements of the evoked responses from 86 rats (under similar conditions of urethane anaesthesia) gave the mean latency from stimulus application to the start of the first positive wave as 4.2 msec (±0.054 msec SE), the latency to the peak of the first positive wave as 7.2 msec (±0.086 msec SE),

![Figure 3](https://academic.oup.com/bja/article-abstract/45/8/824/294454/824)

Fig. 3. Illustration of the variability of the cortical response in an animal sufficiently deeply anaesthetized with urethane to abolish reflex withdrawal. (a) 16 consecutive responses to supramaximal electrical stimulation of the forepaw (1/sec) shown superimposed together with their average (lower record of each pair). In (b) only responses with a small first negative wave have been collected and superimposed (8 responses) plus their average and in (c) responses with large first and second negative waves (8 responses). Record (d) shows a 100-μV, 10-msec calibration for both superimposed and averaged responses. In this and subsequent figures positivity at the active electrodes is shown as an upward deflection. S stimulus artefact; P₁ first positive wave; P₂ second positive wave; N₁ first negative wave; N₂ second negative wave.
and to the trough of the first negative wave as 8.7 msec (±0.086 msec SE); to stimulation of the contralateral forepaw.

At the starting level of anaesthesia (see Methods) the responses obtained from the short latency area were not constant but varied from moment to moment in amplitude, shape and latency (fig. 3a). As the depth of anaesthesia was progressively increased three characteristic changes in the evoked response were always seen irrespective of the anaesthetic agent used. Firstly, there was a progressive increase in the latency of the response. In most cases the latency increased by 1.5–2 times the starting level when a very deep state of anaesthesia was reached. For example, the experiment illustrated in figure 4 showed a change in latency from 4.5 msec to 8.3 msec from a starting level of 1.3 g/kg urethane to a deeper level of 3.25 g/kg. Second there was a progressive decrease in the amplitudes of the major components of the evoked response. This was seen first as an abolition of the second negative wave—if present (fig. 4, A, C) followed by a progressive decrease in the amplitude of the second positive wave (fig. 4, E–G), then the first negative wave and finally the first positive wave until, in very deep anaesthesia, the cortical response was composed of a small, long latency, low amplitude positive wave (fig. 4, D, H). Thirdly, as the depth of anaesthesia was increased the responses became more stereotyped in latency, shape and amplitude. These changes are illustrated for urethane and pentobarbitone anaesthesia in figure 4. Recovery of the latency, variability and amplitude of the cortical response after the last incremental dose of anaesthetic, to the starting level was usually complete within 15–20 min for trichloroethylene, and within 60 min for pentobarbitone. Partial recovery was seen with urethane after a much more prolonged time, 2–3 hours (fig. 5).

Exactly the same pattern of change in the evoked response was seen if "natural" stimulation (brief mechanical tap applied to a digit or paw pad) of
the periphery was used. A comparison of the responses to electrical and natural stimuli is shown in figure 5 for an animal anaesthetized with urethane.

**Chronic experiments.** The cortical responses to hindlimb stimulation in the rabbit with implanted electrodes showed the same features as those of the chronic rat preparation, namely an initial positive wave ($P_1$, fig. 6a) a later second positive wave ($P_2$, fig. 6a), these two separated by a negative wave or inflexion ($N_1$, fig. 6a). In the awake animal the averaged cortical responses were found to vary according to the amount of interest the animal was taking in its surroundings, and the experimental procedure. This variation was found to be most clearly marked in the amplitude of the first negative wave of the cortical response. Basically, the rabbits, in the experimental position, took up one of three

(a) ••
(b) •
(c) •

*FIG. 6. This shows the averaged cortical responses to 120 consecutive electrical stimuli (1/sec) applied at the ankle of a rabbit with electrodes implanted over the hindpaw primary receiving area, before (column a) and after (columns b and c) the animal was quickly deeply anaesthetized with a mixture of trichloroethylene vapour in air; between (a) and (b). The three averages in (a) represent (from top to bottom) the animal resting quietly with ears lowered, resting quietly with ears raised and actively searching its surroundings. The records in column (b) are the responses recorded from the deeply anaesthetized animal with no reflex withdrawal (top) to the "lightly" anaesthetized state with sluggish reflexes (bottom). Those in column (c) are averages taken when the animal was barely anaesthetized with brisk flexion reflex (top) unanaesthetized but "dopey" (middle) and 24 hours after the administration of anaesthetic (bottom). Time scale shows 5-msec divisions, voltage calibration represents 100 μV. Stimuli applied at the thick vertical lines.*

postural attitudes: either (i) they lay quietly in the hammock with their ears flat upon their backs, (ii) they lay quietly with ears raised, or (iii) they actively searched their surroundings, frequently attempting to see what was happening to their stimulated appendage. In these three positions the size of the first negative wave of the cortical response was found to be between 10–20%, 30–50% or 70–90% of the size of the first positive wave, respectively (fig. 6a). These changes in the evoked cortical response occurred even though the amplitude of the ascending volley in the sciatic nerve, monitored at the same time, remained constant.

During the administration of and subsequent recovery from anaesthetic agents the averaged cortical responses underwent a cyclic series of changes. The first effect seen during induction of anaesthesia was an increase in the amplitude of the first negative wave which was accompanied by behavioural exci

*FIG. 7. Averaged cortical responses from a rabbit with implanted electrodes to 120 consecutive electrical stimuli applied to the hindleg (1/sec) showing the excitatory effect of induction of trichloroethylene anaesthesia. (A) animal alert and awake. (B) during the hyperexcitable phase of anaesthesia—the animal jerked to most stimuli. (C) animal deeply anaesthetized, flexion reflexes abolished. Time scale shows 10-msec intervals, voltage calibration represents 100 μV. Stimulus applied at S.*
tion, in which the animal often jerked to each peripheral stimulus. At the same time as the increase in the amplitude of this component of the cortical response the latency became decreased. This effect is illustrated in figure 7. Since this state was only seen if the anaesthetic was administered slowly and we did not wish the animals to come to any harm, in most experiments the deeper states of anaesthesia were attained as quickly as possible. With deepening depth of anaesthesia the amplitude of the first negative wave of the response became progressively reduced with little or no change in the amplitude of the first positive wave and only a slight increase in the latency of the response. Further increase in depth of anaesthesia led to a progressive reduction in the amplitude of the first positive wave of the cortical response, and during this stage, a marked increase in the latency of the response. During recovery from anaesthesia the changes were reversed. Figures 6 and 8 show the cortical responses in two representative experiments, one for trichloroethylene anaesthesia showing recovery (fig. 6) the other for urethane for increasing depth of anaesthesia (fig. 8).

Angel (1967a) and Unwin (1971) have shown that the first positive wave of the cortical response evoked by contralateral forepaw stimulation in the anaesthetized rat is directly proportional to the amplitude of the mass response recorded at the same
time, in the ventrobasal thalamus. This component of the cortical response can, therefore, be used as a rough measure of the ascending (thalamo-cortical) volley. The amplitude of the first negative wave of the cortical response is directly related to the discharge probability of somato-sensory cortical neurones which respond during this wave (Angel and Unwin, 1968) and can be used, therefore, as an indication of the initial cortical output. Thus plotting the amplitude of the first positive wave versus the first negative wave of the cortical response can be used as a measure of the input:output relationships for the cerebral cortex, and show more easily the cyclic changes occurring during induction and recovery from anaesthesia. The effects of pentobarbitone as the anaesthetic are shown in this fashion in figure 9. The measurements taken from the awake animal lying quietly in the hammock before anaesthesia are shown by circles, those for the animal actively searching its surroundings by triangles. The animal was then quickly deeply anaesthetized (50 mg/kg). The responses obtained under deep anaesthesia, with all reflexes abolished, are represented by the large dots. During recovery from the anaesthetic the responses have been arbitrarily divided into two phases, those obtained with sluggish reflexes (○) and those when the reflexes were brisk and caused behavioural arousal (■). Finally the responses from the quiet and active animal 24 hours later are shown, as □ and ▲ respectively.

In all the animals studied for all three anaesthetic agents similar graphs were obtained, although for urethane recovery of the cortical response was only slight before the animal was given a lethal dose of this anaesthetic.

**Blood pressure and respiratory measurements.**

The changes observed in the evoked potential by increase in anaesthetic depth may result from a direct action of the anaesthetic agent blocking central pain transmission of information or altering the responsiveness of the cerebral cortex to an unchanged thalamo-cortical volley. Alternatively the anaesthetic may exert an action on either blood pressure or respiration and the central nervous effect may be as a consequence of an alteration of these functions. For example, Beecher, McDonough and Forbes (1938) showed that a reduction in blood pressure had the same effect as an increase in anaesthetic depth on the cortical response evoked by sciatic nerve stimulation in the cat. Thus a series of experiments have been performed to determine the effect of the three anaesthetic agents on blood pressure and respiratory function.

**Blood pressure.** In 8 rats it was found that no significant change in diastolic and systolic pressures occurred in animals anaesthetized with urethane in doses between 1.25–3.2 g/kg. However, in a further 8 rats, 4 anaesthetized with trichloroethylene and 4 with pentobarbitone, the mean blood pressure fell by approximately 50% from the starting level of anaesthesia (reflex withdrawal just abolished, approx. 2% and 30 mg/kg respectively) to the finishing level (i.e. at which point the cortical response was almost abolished, approx. 6% and 85 mg/kg respectively).

**Respiratory function.** With all three anaesthetic agents respiratory rate and tidal volume were decreased as the depth of anaesthesia increased. For example, in a group of 6 rats the tidal volume fell from a mean value of 0.9 ml (urethane 1.25 g/kg) to 0.4 ml (urethane 3.2 g/kg). These changes in rate and tidal volume were accompanied by changes in the composition of arterial blood-gases. In all cases arterial Po₂ (measured in 4 animals for each of the three anaesthetic agents used) fell from a mean value of 67 to 46 mm Hg (pentobarbitone); from 84 to 64 mm Hg (trichloroethylene); and from 95 to 49 mm Hg (urethane). Arterial Pco₂ only rose significantly in the animals anaesthetized with pentobarbitone, from a mean value of 45 to 71 mm Hg. (Each pair of figures above refers to the starting level of anaesthesia; reflex withdrawal just abolished and the finishing level evoked responses almost abolished.) With trichloroethylene and urethane no statistically significant difference at the 5% level was found for the starting and finishing levels of arterial Pco₂.

**Respiratory controls.** Thus the possibility arose that the changes seen in the evoked cortical response could be produced by hypoxia. Two types of control experiments were performed, therefore, to check this possibility in animals anaesthetized with urethane. In one, the experiments (12 in number) were repeated with the animals spontaneously respiring a 95% oxygen, 5% carbon dioxide gas mixture, in the second the animals (12 in number) were curarized and artificially ventilated at a rate and depth matched visually to the animal's starting level. Analysis of carotid arterial blood showed that the artificially ventilated animals were all overventilated since Po₂ rose (from 95 to 123 mm Hg) and Pco₂ fell (from 42 to 20 mm Hg). The results obtained from these two types of experiment were
FIG. 10. The effect of urethane anaesthesia in three different acute rat preparations under three different respiratory conditions. One animal was breathing room air, 1 a mixture of 95% oxygen, 5% carbon dioxide spontaneously, and 1 was curarized and artificially ventilated. Cumulative dose of urethane (g/kg) shown on the left refers to the three records in each row.

FIG. 11. Absence of effect of increasing anaesthetic dose in an animal showing signs of cerebral oedema. A and C records obtained from oedematous and normal cortices respectively. Each trace is the average response to 60 consecutive 1/sec electrical stimuli applied to the wrist. The vertical lines indicate the cortical response latency at the start of the experiment, i.e. time before first additional dose of anaesthetic. The mean size of the first positive wave of the responses is plotted in B (○ oedematous, ● normal) versus the cumulative dose of urethane. The graph with crosses represents the results from the most susceptible animal, those for the least susceptible animal, dots. Length of averaged responses represents 10 msec. Vertical distance between first and last responses in A represents 2 mV. The vertical lines in A and C indicate the latency of the first response.
Effects of cerebral oedema. In some experiments (irrespective of the anaesthetic) it was noticed that no marked change in the cortical response accompanied increased depth of anaesthesia. In such animals slight or marked signs of cortical swelling (oedema) were seen. One example of such an experiment is shown in figure 11 in which increasing the depth of urethane anaesthesia from 1.25 to 5.0 g/kg produced no effect on the size of the first positive wave of the cortical response or its latency.

DISCUSSION

Previous studies on the effect of anaesthetic agents on the cortical responses evoked by peripheral stimulation have been inconclusive. Derbyshire and associates (1936), French, Verzeano and Magoun (1953), Abrahamian and associates (1963) and Lader and Norris (1968) found no effect while Brazier (1953), Dawson, Podachin and Schatz (1963), Domino, Corssen and Sweet (1963) and Angel (1967b) showed that the cortical response was altered by anaesthesia. The above may be simply explained by differences in anaesthetic agent used or by difference in the animals used. Therefore in the present investigation, two orders of mammals were used, one a member of the Lagomorpha, the other of the Rodentia, and additionally three completely different anaesthetic agents. Initially a group of experiments was performed to locate accurately the primary receiving area of the cortex, defined as that area from which responses with the shortest latency, plus 12.5% of this shortest time (i.e. in most experiments latencies between 4-4.5 msec) could be obtained to stimulation of a contralateral limb. This area was considered to be the most important to study since it is the first to receive the ascending information. The area of cortex giving the shortest latency responses to contralateral forepaw stimulation in the rat at the starting level of anaesthesia (see Methods) was found to be a rectangle of sides 1 x 2 mm, orientated with its long axis at an angle of 20-30° from the medio-lateral plane near a blood-vessel fork on the cortical surface. The centre of the short latency area lay 3 mm lateral and 2 mm anterior to the intersection between the coronal and sagittal sutures. This agrees with earlier experiments of Angel (1962, 1967a), who used the same anaesthetic (urethane) and stimulating arrangements, but disagrees with the results of Dawson and Holmes (1966) with the same anaesthetic but a different stimulating arrangement. In the experiments reported here stimuli were applied to the forepaw with the negative electrode wrapped around the wrist and the positive electrode wrapped around the fourth digit. This arrangement ensures that the whole of the contralateral forepaw cortical area is activated by coincident stimulation of the radial, medial and ulnar nerves. The experiments of Dawson and Holmes (1966), which gave the short latency area as an oval 2 x 0.5 mm located in approximately the same region of the cortex but orientated with its long axis in the rostro-caudal axis, were performed with the stimulating electrodes wrapped around the second and fourth digits of the contralateral forepaw. This stimulating arrangement would tend to give varying degrees of anodal block as well as excitation of the nerves depending upon the strength of stimulation, polarity and spatial location of the electrodes. This, in fact, could explain the different results since a different and varying portion of the "forepaw" area may have been activated. However, because of this discrepancy an attempt has been made to determine the orientation of the area more accurately. The methods used were to plot the response for the cortex in a stereotaxic grid and to assume that the cortical elements made active by the incoming volley could be considered as a simple dipole. Employing Gaussian analysis it was found that the orientation was the same as that indicated by the mapping experiments. Since both results were in agreement it would seem that the co-activation of a large population of nerve cells by a synchronous afferent volley can be considered as generating a theoretical single dipole, hence it may be possible to apply this method in other situations. The centre of the short latency area was found to be in the same location regardless of the anaesthetic agent used although its extent was found to vary slightly (Angel, 1967a).

Eidelberg and Jenkins (1966) showed that the cortical area from which a response could be obtained to stimulation of the hand in monkey became progressively smaller when the depth of pentobarbitone anaesthesia was increased. Thus the decrease in cortical responses obtained in the present study could be explained by the fact that if the recording electrodes were not accurately located...
over the centre of the short latency area a possible decrease in the size of the area could move the active area further away from the recording electrode and result in a passive decrease in response size. This possibility was eliminated by a group of experiments in which the short latency area was mapped at two anaesthetic levels. The short latency area was, in fact, found to be increased in size at the deeper level of anaesthesia. If one accepts the definition of short latency area as given above it is clear that the effect of an increase in anaesthetic depth is to increase the overall volume of cortical tissue to which the afferent volley gains access, albeit with a diminished power of excitation of the cortical neuronal elements (shown as a decrease in the amplitude of the cortical response). The decrease seen in the amplitude of the cortical response supports the findings of Brazier (1953), Dawson, Podachin and Schatz (1963), Domino, Corssen and Sweet (1963) and Angel (1967b). This decrease in amplitude was also seen in chronic experiments in rabbits when the animals were taken from a state of wakefulness to one of deep surgical anaesthesia.

The chronic experiments also showed that during induction of anaesthesia the evoked response underwent a transient increase in amplitude and decrease in latency accompanied by behavioural excitation. A transient small excitatory phase was sometimes observed in anaesthetized rats immediately after a further dose of anaesthetic. This excitatory phase during induction of anaesthesia has also been reported by Brazier (1953) and is a well-known clinical phenomenon for some anaesthetic agents. On some occasions, especially with trichloroethylene anaesthesia, induction caused the animals to jerk in response to each peripheral stimulus; in these cases the first negative wave of the cortical response was found to be markedly increased in size (fig. 7). It is of interest to note here that in a patient with sensory myoclonus the negative wave of the cortical responses was enhanced when the patient was jerking but of normal amplitude when no jerking occurred (Halliday, 1967). A phase of excitation was also seen in the chronic experiments when the animal was recovering from the anaesthetic, although this was less marked than in the inductive phase.

This decrease in the amplitude of the evoked response in both acute and chronic experiments was accompanied by an increase in latency and a trend for the responses to lose their variability. That is, at the deeper levels of anaesthesia the responses became more stereotyped in amplitude, latency and form. Several possible explanations can be put forward to explain these effects of anaesthesia: (a) there is a decrease in the centripetal transfer of information at any or all three sites of synaptic transmission in the dorsal column medial lemniscal sensory pathway i.e. the dorsal column nuclei, the ventrobasal thalamus or the somato-sensory cortex; (b) the responsiveness of the cortex itself to the afferent volley, may be decreased; (c) these changes may be secondary to respiratory or circulatory changes produced by anaesthesia; or (d) any combination of these three.

We have been able to rule out the possibility that the cortical responses are changed as a result of circulatory and respiratory changes by the control experiments performed in this investigation. Of the three anaesthetic agents used only two (pentobarbitone and trichloroethylene) caused a fall in blood pressure, whereas all three produced, qualitatively, the same effect on the cortical response. Moreover, pentobarbitone and trichloroethylene even in sufficient amounts to produce deep surgical anaesthesia did not reduce the mean blood pressure by more than 50% of its starting level so that it is possible that the intrinsic control over cerebral blood flow would not be impaired (Lassen, 1959). However, one consistent respiratory change was seen. All three anaesthetic agents reduced arterial oxygen tension by approximately 50% at the deepest levels of anaesthesia. Thus one has to rule out hypoxia as the cause of the diminished cortical responses. This was accomplished by showing that all three anaesthetics produced identical effects in the normal animal breathing room air, or in animals spontaneously respiring a 95% oxygen, 5% carbon dioxide gas mixture, or in artificially respired curarized animals, i.e. the effect was the same whether the animals became hypoxic or if the arterial oxygen tension was artificially maintained.

Thus the decrease in the amplitude of the cortical responses to peripheral stimulation in the anaesthetized animal appears to be a consequence of the anaesthetic exerting its effect directly on the central nervous system and not as an indirect consequence of interference with the oxygen supply of the nervous system. The question of the site or sites of action of anaesthetics will be dealt with in the following papers.

One finding for which we can suggest no explanation at present is the lack of the effect of anaesthesia in animals showing signs of cerebral oedema. This question requires a more complete investigation.
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REFERENCES


—— (1967a). Cortical responses to paired stimuli applied peripherally and at sites along the somatosensory pathway. J. Physiol. (Lond.), 191, 427.

—— (1967b). The effect of attention and anaesthesia on evoked somatosensory cortical responses. J. Physiol. (Lond.), 192, 6P.


