Br. J. Pharmac. (1971), **42**, 328–342.

Blockade of the reticulospinal inhibitory pathway by anaesthetic agents

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Summary

1. Adult cats were decerebrated at the intercollicular level. The effect of the anaesthetic agents, pentobarbitone, paraldehyde, tribromethanol, chloralose and procaine on the reticulospinal inhibitory pathway, which produced inhibition of segmental reflex potentials, was analysed.

2. The doses which blocked this inhibitory pathway did not exceed the doses required to produce surgical level anaesthesia with any of the drugs.

3. After the reticular inhibition of the reflex potentials was abolished, the reflex potentials were augmented by reticular stimulation with a higher intensity. This was thought to be due to spread of current to the excitatory pathways which were not completely depressed by the anaesthetic agent.

4. The resistance of the reticular facilitation of the reflex potentials to inhibition by these drugs after abolition of inhibition corresponded in general to the degree of excitement in intact mice produced by the same drugs.

5. These findings seem to indicate that the preferential block of the reticulospinal inhibitory pathway may be an important neural mechanism for the excitement stage of anaesthesia.

Introduction

Magoun and his co-workers (Moruzzi & Magoun, 1949; French, Verzeano & Magoun, 1953) demonstrated that the central cephalic brain stem was important for the maintenance of wakefulness, and was highly susceptible to ether and pentobarbitone. They proposed that depression of this region was the neural basis for the production of the anaesthetic state.

Their findings have been confirmed by other investigators using the same and other anaesthetic agents (Arduini & Arduini, 1954; Brazier, 1961; Davis, Collins, Randt & Dillon, 1957; Davis, Quitmeyer & Collins, 1961; Killam, 1962; King, 1956). However, most investigations have concentrated on the ascending reticular system and only a few studies have been reported concerning the effects of anaesthetics on the descending reticular system (Brooks, Koizumi & Siebens, 1956; Valdman & Arushanyan, 1967).

Muscular tone increases as consciousness decreases in the lighter stages of anaesthesia, and a depression of the resting level of inhibition of the extrapyramidal system by the anaesthetics was proposed by Ngai (1963) to explain this phenomenon. In this paper, to test the possibility that the excitement stage of anaesthesia is caused by the preferential block of inhibitory pathways, the effect of some anaes-

thetic agents on the reticulospinal inhibitory pathway was investigated. All of the tested anaesthetic drugs, in doses below those required to produce the surgical level of anaesthesia, could abolish the reticular inhibition of segmental reflex potentials. Some of the results have been reported previously (Ohta & Frank, 1970).

Methods

Adult cats, 2–3·5 kg in weight were decerebrated at the intercollicular level after clamping of both carotid arteries under ether anaesthesia, which was discontinued just before or after decerebration. Laminectomy was made and the ventral roots from L5 to L7 were cut to reduce the movements at the time of dorsal root stimulation.

Segmental reflex potentials were recorded from the L6 ventral root responding to the electrical stimulation of the ipsilateral L6 dorsal root once every 1–2 seconds. Stimulus parameters were 0·2 ms and about 3·5 V (range 2–8 V, but usually less than 5 V). The recorded reflex potentials were compared before, during and after reticular stimulation at a frequency of 100 Hz for 15 seconds. The ipsilateral bulbar reticular formation (P.10.0 ; L.1.0 ; D.$-7{\cdot}0\sim-8{\cdot}5$; stereotaxic coordinates by Snider & Niemer, 1961) was electrically stimulated through a stereotaxically orientated bipolar platinum wire electrode with square wave pulses 2·5 ms in duration and about 5 V and at a frequency of 100 Hz for 15 s (Fig. 1).

The anaesthetic agents, pentobarbitone, paraldehyde, tribromethanol, chloralose and procaine were administered intravenously with gradually increasing doses, and the total doses were plotted in the graphs.

The rectal temperature was controlled at around 36° C (± 1° C) and artificial respiration was used only occasionally when the breathing of the animal was much reduced or ceased due to the action of high anaesthetic doses. The results obtained in the few animals requiring artificial respiration did not differ from those obtained with the other animals.

The size of the polysynaptic reflex response was measured as the maximum potential amplitude recorded during the polysynaptic discharge. Although another measure, such as the area under the discharge, might be a more precise measure of the polysynaptic discharge size, the measurement we used was considered to be satisfactory and sufficient for the purposes of our experiments.

Results

Reticular inhibition of the segmental reflex potentials

The segmental reflex potentials recorded from the sixth lumbar ventral root consist of a monosynaptic spike and a few polysynaptic waves (Figs. 3, 5, 7, 9 and 11).

Both monosynaptic and polysynaptic ventral root potentials were greatly reduced immediately after the start of repetitive stimulation, with adequate intensity, of the reticulospinal inhibitory area; they rapidly recovered to their control amplitudes after cessation of reticular stimulation (Fig. 1). The segmental reflex potentials were usually maximally inhibited at about 6 or 7 s after commencing the reticular stimulation. Therefore in the experiments described here, the effect of each drug on this reticular inhibition was analysed by determining the mean of the reflex

potentials recorded during the period from 5 to 10 s after the start of reticular stimulation.

Pentobarbitone

The monosynaptic potential decreased progressively with increasing doses of pentobarbitone. The polysynaptic potentials were not depressed but slightly augmented with small doses and then progressively reduced with further increasing doses (Figs. 2 and 3). As can be seen from Fig. 2, the monosynaptic reflex potentials were more sensitive to depression and block by pentobarbitone than the polysynaptic potentials.

The reticular inhibition of the reflex potentials was progressively reduced and finally abolished by pentobarbitone (Fig. 2). The reticular inhibition of the polysynaptic potentials was reduced by pentobarbitone at doses lower than those required for reduction of inhibition of the monosynaptic potentials. The reticular inhibition of the monosynaptic potentials was abolished by pentobarbitone at a dose level of about 5 mg/kg above that which blocked the reticular inhibition of the polysynaptic potentials.

After the reticular inhibition was abolished, facilitation of the reflex potentials was observed frequently during reticular stimulation by the same electrodes but with

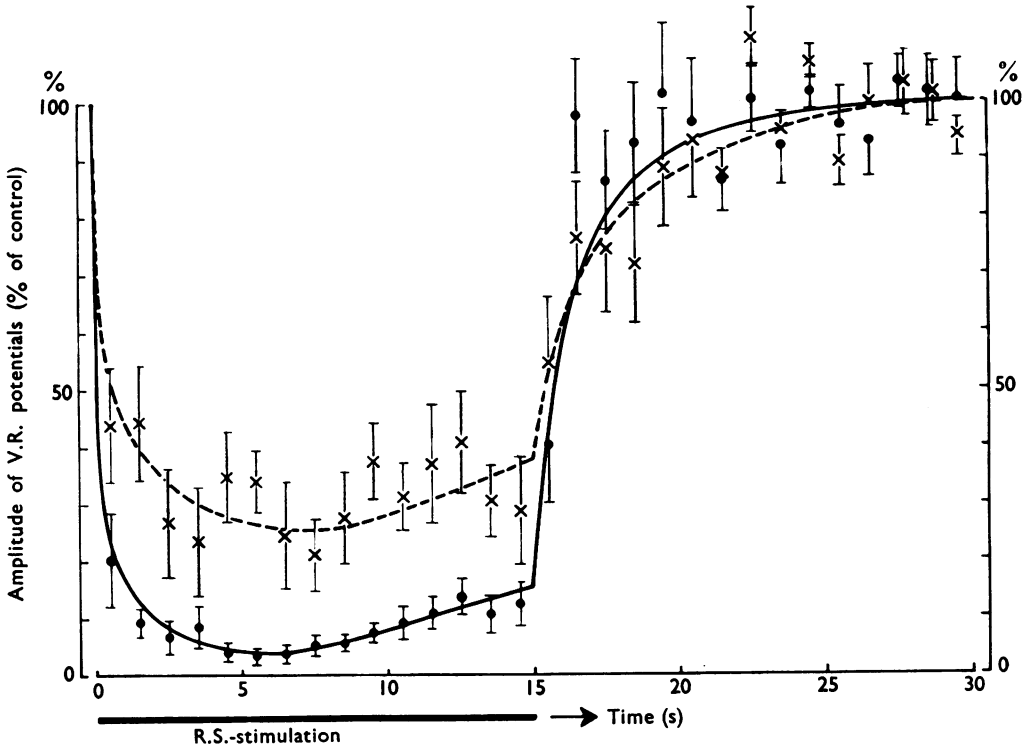

FIG. 1. Effect of adequate stimulation of the reticular formation on the segmental reflex potentials. Means of results obtained from six tests in cats ± the standard error (vertical bars). The mean of control monosynaptic potential (●) (100%) was 1·67 ± 0·45 mV and the mean of control polysynaptic potential (X) (100%) was 0·164 ± 0·052 mV. R.S. the reticulospinal inhibitory region, and V.R., the ventral root. Further explanation in the text.

a higher intensity (Fig. 3 ; 10 mg/kg). This was probably caused by the spread of current to excitatory regions in the vicinity of the inhibitory region. This reticular facilitation of the reflex potentials was abolished by a much higher dose of pentobarbitone than that required to block the reticular inhibition. The phenomenon was observed with every drug tested in this investigation.

Paraldehyde

The monosynaptic potential was progressively depressed by increasing doses of paraldehyde. The polysynaptic potentials increased very slightly with small doses and then progressively decreased with higher doses.

This would suggest that the sensitivity of the segmental reflex pathways to pentobarbitone or paraldehyde does not depend on the number of synaptic connexions in series in their pathways. The same phenomenon was also reported by DeJong,

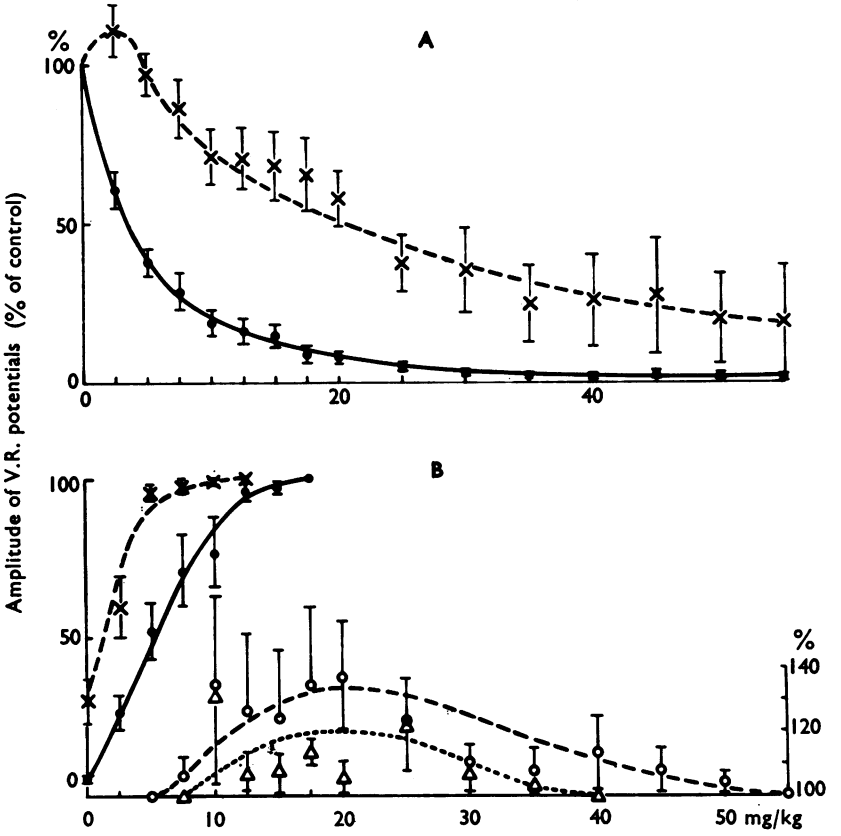

FIG. 2. Effect of pentobarbitone on the segmental reflex potentials is shown in A (without R.S.-stimulation). Each dot (monosynaptic) and cross (polysynaptic) indicate the mean of seven observations. B (during R.S.-stimulation) illustrates the effect of pentobarbitone on the reticular inhibition (curves on the left) and facilitation (curves on the right). The dot and across indicate each mean of the inhibited monosynaptic potentials and polysynaptic ones, respectively, and 100% indicates a complete loss of inhibition. The open circle and the open triangle indicate the augmented monosynaptic and polysynaptic potentials, respectively, during reticular stimulation with a higher intensity (shown by the means of three observations). The baseline for the reticular facilitation (calibration at the right) is 100% which indicates a lack or a complete block by higher doses of pentobarbitone of the excitatory pathways.

Robles, Corbin & Nace (1968) with some gaseous and volatile anaesthetics. On the other hand, Preston (1957) found that the monosynaptic potential was much more resistant to pentobarbitone than the polysynaptic potentials. However, his experiments were made in acute spinal cats, presumably with some degree of spinal shock, and thus the discrepancy might be due to the differences in the conditions of the preparations used in the various studies.

The reticular inhibition of both reflex potentials was not altered by the small doses of paraldehyde (100–150 mg/kg) but was reduced with higher doses and finally abolished by a total dose of about 300 mg/kg (Fig. 4). Depression of the reticular inhibition by paraldehyde began at the same dose which first produced a reduction of the polysynaptic potentials, but the polysynaptic potentials were still observed after the reticular inhibition was abolished.

After the reticular inhibition was completely blocked, facilitation of the reflex potentials was observed in some cases but this facilitation was very small (Fig. 4).

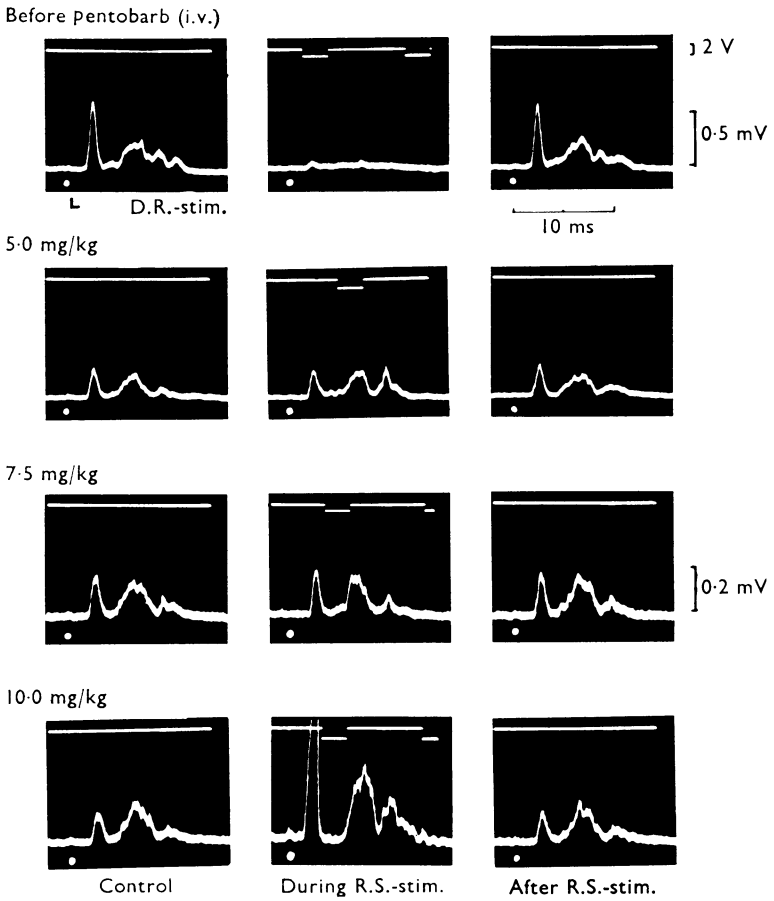

FIG. 3. Effect of pentobarbitone on the reflex potentials before (left-hand figures), during (centre figures) and after reticular stimulation (right-hand figures). The upper line in each figure indicates the reticular stimulation and the baseline shows the segmental reflex potentials. Dorsal root stimulation which is marked by white dots produced a monosynaptic and a few polysynaptic potentials. In this case 7·5 mg/kg of pentobarbitone completely blocked the reticular inhibition and then reticular stimulation with a higher intensity greatly augmented both reflex potentials (as shown in the lowest central figure). The amplification in the lower two rows of records is twice as much as that in the upper two rows.

Tribromethanol

Tribromethanol was administered in Tyrode's solution up to a total dose of 100 mg/kg and with tertiary amyl alcohol in further doses because of poor solubility in water. The effects of tertiary amyl alcohol were tested without tribromethanol, and both reflex potentials as well as the reticular inhibition were unchanged by the amount (0·05~0·1 ml) which would contain each additional dose (25 mg/kg) of tribromethanol. However, 0·25 ml of this alcohol depressed the reflex potentials by 10~25% and slightly reduced the reticular inhibition by 2~13%. This depression of the reticulospinal system seems to be due to the respiratory disturbance produced by this dose of the amyl alcohol, since artificial respiration was necessary a few minutes after its administration, and additional administration had a fatal toxic effect on the animal in which the reflex potentials as well as the reticular influences were abolished.

An initial small dose of tribromethanol (10 mg/kg) augmented the monosynaptic potential very slightly and higher doses reduced it progressively. The polysynaptic potentials were depressed by all tribromethanol doses (Fig. 6).

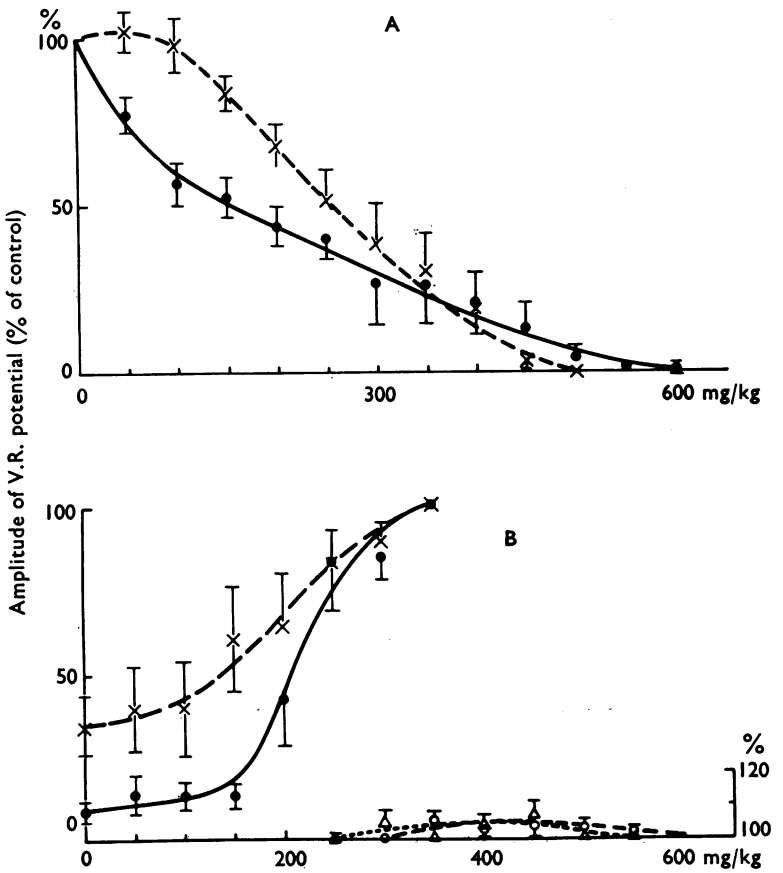

FIG. 4. Effect of paraldehyde on the segmental reflex potentials is shown in A (without R.S.-stimulation) and that on the reticular inhibition and facilitation in B (during R.S.-stimulation) as in Fig. 2. Each point indicates the mean of five observations. Monosynaptic potentials (●), polysynaptic potentials (×).

The reticular inhibition of both reflex potentials was depressed and finally abolished by about 80 mg/kg tribromethanol. After the reticular inhibition was abolished, reticular stimulation with a higher intensity frequently augmented both reflex potentials. This facilitation was smaller than that observed in the case of pentobarbitone, chloralose or procaine. However, depression of this reticular facilitation may be partially (less than 20%) due to amyl alcohol. Nevertheless, block of the reticular inhibition of the reflex potentials was produced solely by the tribromethanol.

Chloralose

Chloralose was administered in a 10% solution with polyethylene glycol 200. It augmented the monosynaptic potential slightly at fairly low doses and depressed it gradually at higher doses. The polysynaptic potentials were very slightly augmented at an initial small dose (10 mg/kg) and depressed progressively with increasing

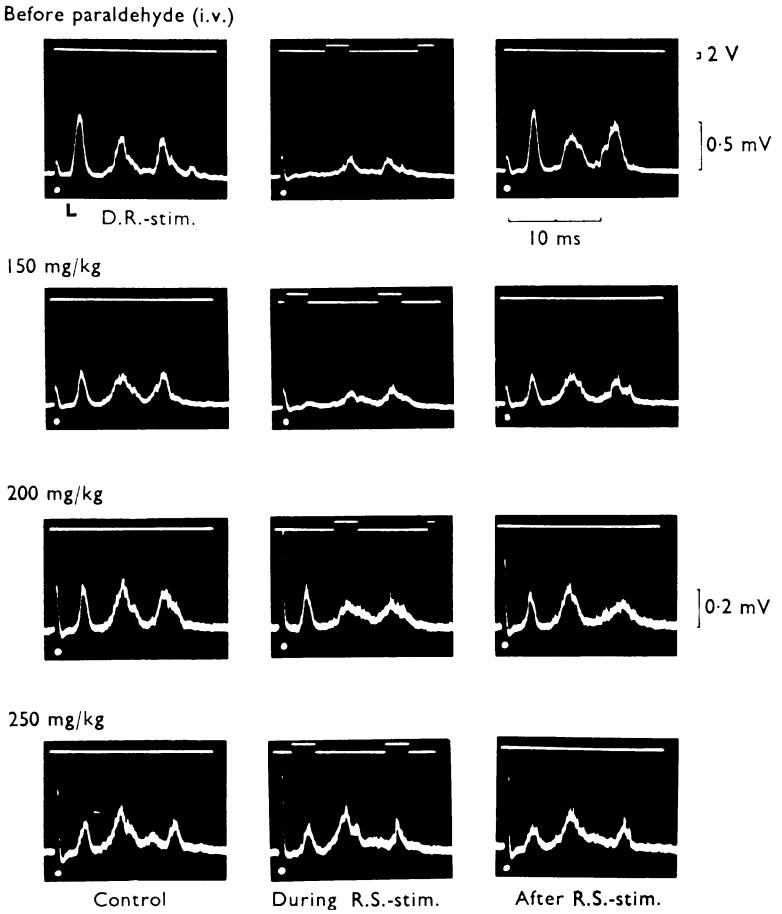

FIG. 5. Effect of paraldehyde on reflex potentials. Paraldehyde (200 mg/kg) blocked the reticular inhibition of the monosynaptic potential and 250 mg/kg abolished the reticular inhibition of the polysynaptic potential. The reflex potential was slightly decreased 15 min after a total dose of 250 mg/kg of paraldehyde and thereafter continued to decrease. For this reason, in the lowest row of figures, the reflex potentials did not completely recover to the control amplitude after the reticular stimulation. The amplification in the lower two rows is twice as much as that in the upper two rows.

doses (Fig. 8). Part of the depression of the reflex potentials was probably due to polyethylene glycol, because doses of 0·5–1 ml of polyethylene glycol (that is the amounts used with chloralose) when tested without chloralose reduced both reflex potentials by 13–20%. Polyethylene glycol had no effect upon the reticular inhibition of the reflex potentials.

Chloralose depressed and finally abolished the reticular inhibition at a dose of 50–100 mg/kg in various animals. After the reticular inhibition was completely blocked, the monosynaptic potential was always augmented and the polysynaptic ones were frequently facilitated by reticular stimulation with a higher intensity. This facilitation of the reflex potentials was abolished by very high doses of chloralose.

Procaine

The monosynaptic potential was augmented by fairly low doses of procaine and was gradually and progressively reduced by higher doses. The polysynaptic potentials were progressively depressed by all the doses used (Fig. 10).

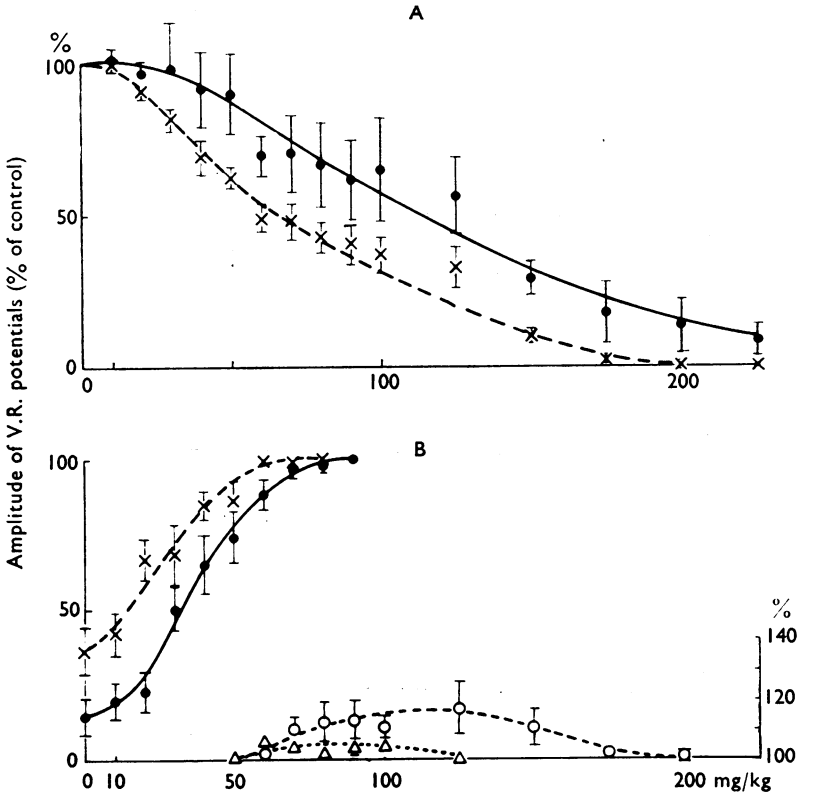

FIG. 6. Effect of tribromethanol on reflex potentials in A (without R.S.-stimulation) and on reticular inhibition (curves on left) and facilitation (curves on right) in B (during R.S.- stimulation): 100% indicates complete loss of inhibition. The scale for the facilitation curves is given on the right hand side of the lower diagram. Up to a dose of 100 mg/kg, tribromethanol was administered with Tyrode's solution and further doses with tertiary amyl alcohol. Monosynaptic potentials (● and ○); polysynaptic potentials (× and △). Each point indicates the mean of five observations.

Augmentation of the monosynaptic potential by low doses of chloralose and procaine may be due to a depression of segmental and/or suprasegmental inhibitory pathways. The same phenomenon was reported by DeJong, Robles & Corbin (1969) with lignocaine and also by Simamura, Yamauchi & Aoki (1968) with chloralose.

The reticular inhibition of the monosynaptic potential was very rapidly depressed and abolished by small doses of procaine. The reticular inhibition of the polysynaptic potentials was greatly depressed by small doses of procaine, but was abolished only by much higher doses of procaine than were required for block of the reticular inhibition of monosynaptic potentials (Fig. 10).

After the reticular inhibition of the reflex potentials was blocked, considerable facilitation of the monosynaptic potentials and slight facilitation of the polysynaptic potentials were produced by reticular stimulation with a higher intensity. As can be seen from Fig. 10 this facilitation was produced even at doses lower than those required to completely block the reticular inhibition. The facilitation of the mono-

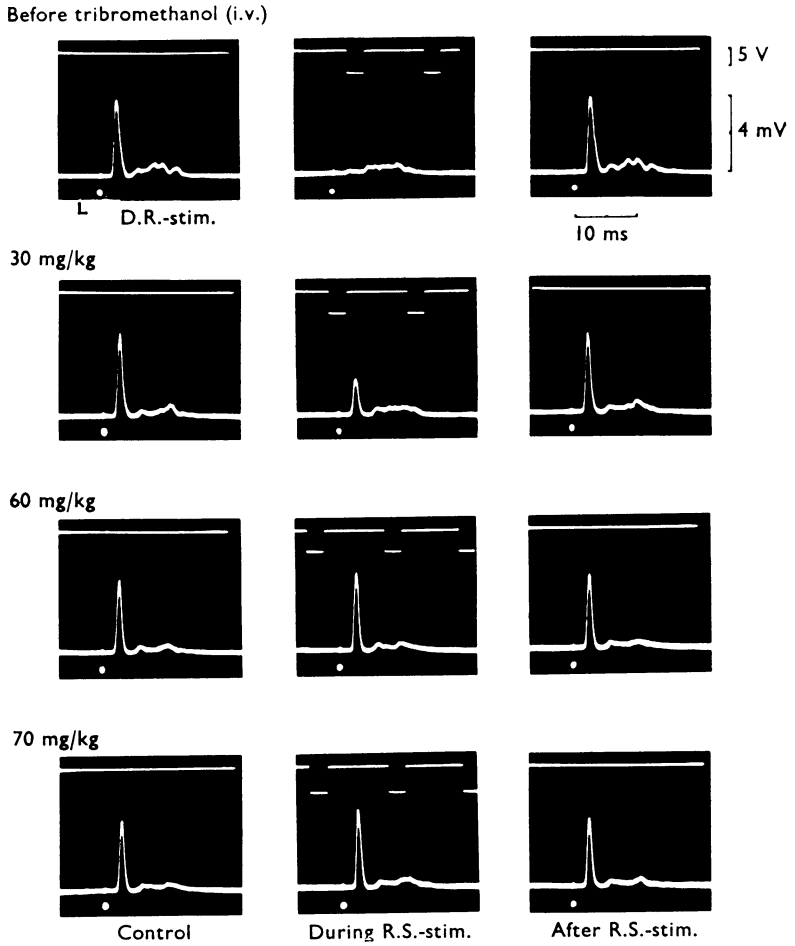

FIG. 7. An example of the effect of tribromethanol. Tribromethanol (60 mg/kg) abolished the reticular inhibition. A slight facilitation of the reflex potentials during reticular stimulation with a higher intensity is shown in the lowest central trace.

synaptic potential was greatest at doses which are considered to be convulsant in the cat (Frank & Saunders, 1963). The reticular facilitation of both reflex potentials was abolished by very high doses of procaine; in some cases total doses of over 200 mg/kg were required.

Occasionally at convulsant doses, both reflex potentials were augmented for a few minutes immediately after each administration of procaine, and simultaneously the animals showed some signs of clonic convulsant movements of the forelimbs.

Discussion

The reticular inhibitory effect on spinal reflexes was first described by Magoun & Rhines (1946) who also reported a reticular facilitatory influence on motor activity (Rhines & Magoun, 1946). The spinal pathways for those reticular influences were investigated by Niemer & Magoun (1947). Brooks and his co-workers (Brooks *et al.*, 1956; Koizumi, Ushiyama & Brooks, 1959; Ushiyama, Koizumi & Brooks, 1960) reported that reticular stimulation altered neither the resting membrane potential

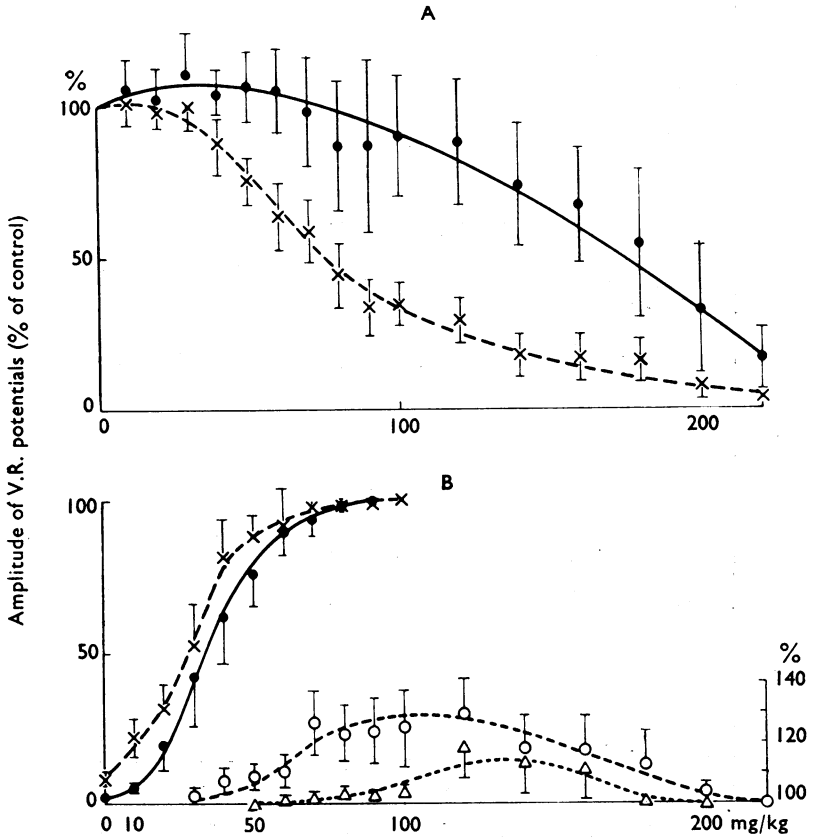

FIG. 8. Effect of chloralose on reflex potentials in A (without R.S.-stimulation), and on reticular inhibition (curves on the left) and facilitation (curves on the right) in B (during R.S.-stimulation): 100% indicates complete loss of inhibition. The scale for the facilitation curves is given on the right hand side of the lower diagram. Monosynaptic potentials (● and ○); polysynaptic potentials (× and △). Each point indicates the mean of five observations.

nor excitatory postsynaptic potential (EPSP) in the spinal motoneurones and that it suppressed interneurones but did not block the afferent terminals on spinal motoneurones. They also suggested that reticular inhibition might be due to a membrane stabilizing effect or hyperpolarization at the dendritic portions in motoneurones.

Lundberg and his co-workers (Lundberg, 1964 ; Carpenter, Engberg & Lundberg, 1962 ; Lundberg & Vyklický, 1963a, b) observed potentials in the dorsal root evoked by reticular stimulation. They suggested that a depolarization in the afferent fibres might occur simultaneously with the dorsal root potentials they were recording and that this depolarization might inhibit the segmental reflex pathway presynaptically as well as the inhibitory postsynaptic potentials (IPSPs) on spinal motoneurones and interneurones, induced by reticular stimulation. However, in a later study (Jankowska, Lund, Lundberg & Pompeiano, 1964), they recorded IPSPs in α-motoneurones simultaneously with the dorsal root potentials evoked by reticular stimulation and concluded that ' in all likelihood the main action is through postsynaptic inhibition on motoneurones '.

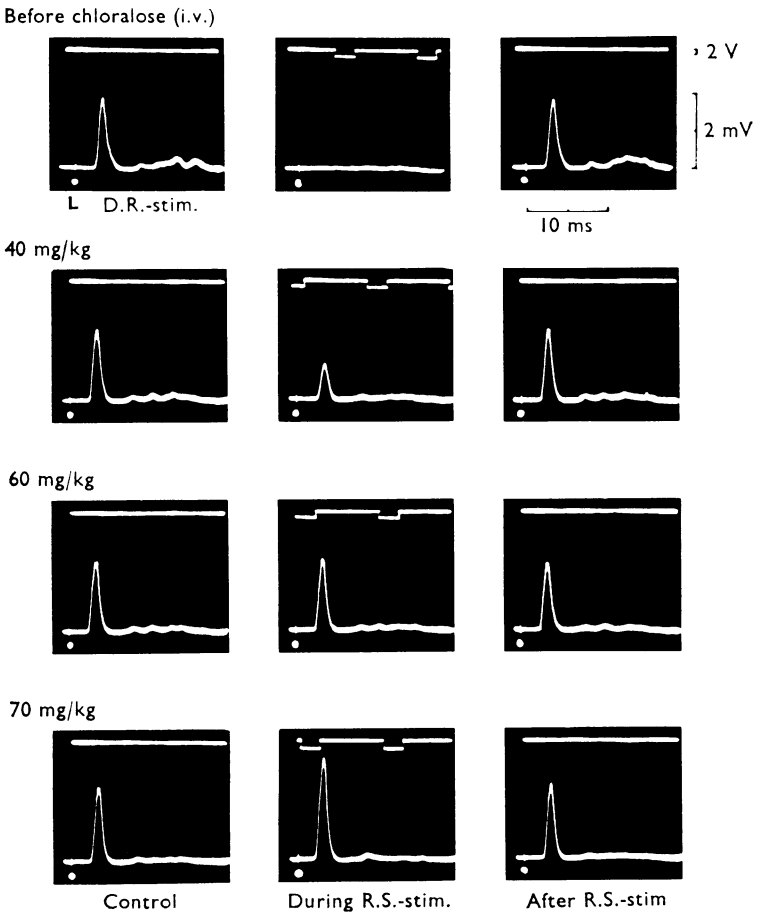

FIG. 9. An example of the effect of chloralose. Chloralose (60 mg/kg) blocked the reticular inhibition, and then reticular stimulation with a higher intensity produced a big facilitation of the monosynaptic potential ; a slight facilitation of the polysynaptic potential is shown in the lowest row.

Willis & Magni (1964) suggested inhibition of interneurones as well as presynaptic inhibition as the immediate cause of the inhibition produced by reticular stimulation.

Llinas & Terzuolo (1964, 1965) using intracellular as well as extracellular recording from the motoneurones, found that adequate reticular stimulation produced a sustained IPSP on motoneurones and they denied the possibility of presynaptic inhibition playing a role in the reticular induced inhibition. They obtained the equilibrium potential for the reticularly induced IPSP of the extensor motoneurones but could not obtain one for the flexor motoneurones. They therefore suggested that the inhibitory synaptic sites activated by reticular stimulation might be on the dendritic portions remote from the cell bodies in the flexor motoneurones.

Llinas (1964) found that strychnine depressed a large part of the reticularly induced IPSP but did not reduce the reticular inhibition of the reflex potentials. But under these conditions an additional small dose of mephenesin would abolish the reticular inhibition. Llinas suggested that the reticular inhibition of the reflex

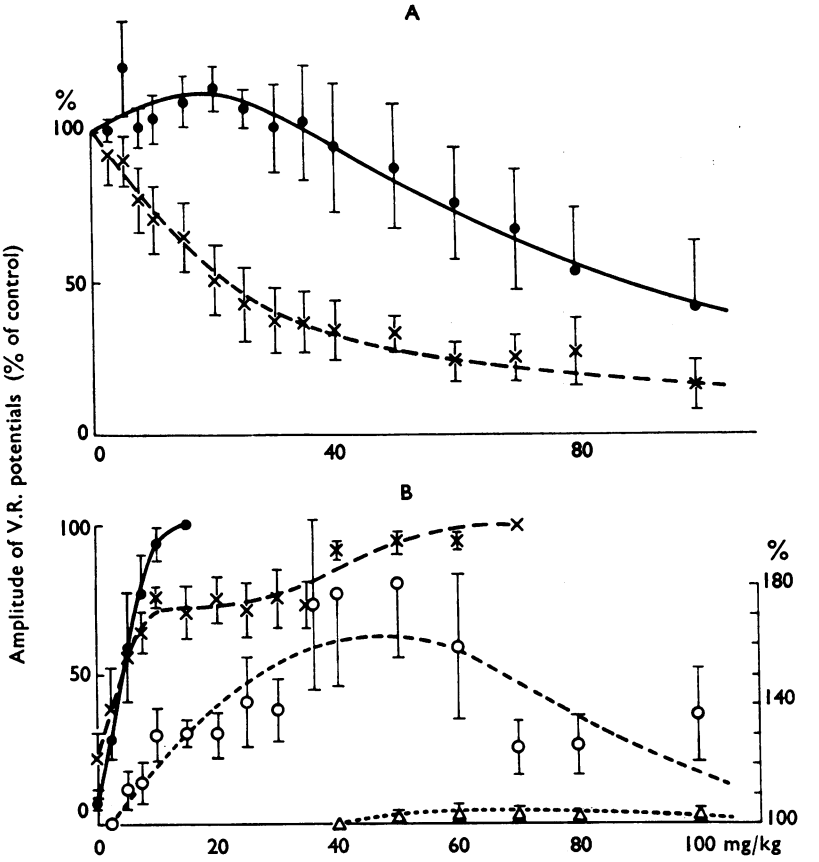

FIG. 10. Effect of procaine on reflex potentials in A (without R.S.-stimulation), and on reticular inhibition (curves on the left) and facilitation (curves on the right) in B (during R.S.-stimulation): 100% indicates complete loss of inhibition. The scale for the facilitation curves is given on the right hand side of the lower diagram. Monosynaptic potentials (● and ○); polysynaptic potentials (× and △). Each point indicates the mean of five observations.

potentials was possibly produced by a reticular inhibitory control of the background excitatory influences on the reflex pathway as well as by the production of an IPSP on the motoneurones.

Evidence that inhibitory pathways may be more susceptible to anaesthetic depression than excitatory pathways was described by Preston & Whitlock (1960) who found that the precentral inhibition of spinal reflexes was much more susceptible to pentobarbitone depression than precentral excitation. But since the precentral excitation is thought to be much more important for corticospinal organization than precentral inhibition, it seems necessary to test a predominantly inhibitory pathway in attempting to explain the excitement stage of anaesthesia.

Brooks *et al.* (1956) reported that pentobarbitone or ether produced no qualitative change in the reticular inhibition of reflex potentials although the control spike heights were greatly reduced by the deepening anaesthesia ; however, they did not make a detailed analysis of the drug effects.

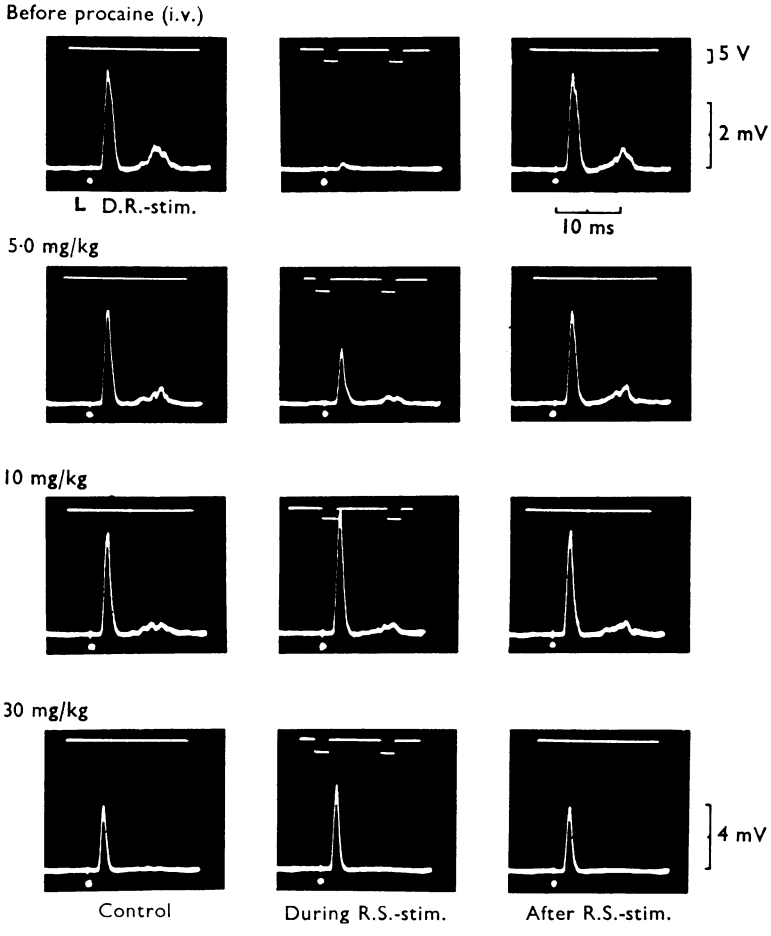

FIG. 11. An example of the effect of procaine. Procaine (10 mg/kg) completely depressed the reticular inhibition, and reticular stimulation augmented the monosynaptic potential. The monosynaptic potential gradually increased with increasing dose of procaine up to 30 mg/kg. Amplification in the two lower rows is twice as much as that in the other rows.

Valdman & Arushanyan (1967) reported that high doses of narcotics could depress suprasegmental inhibition of spinal reflexes. However, they thought that this depression was mainly exerted on the tonic inhibitory impulses arising in the rostral parts of the brain down to the medial reticular formation and that inhibition of reflexes by direct stimulation of the reticular formation appeared to be more resistant to barbiturates.

In this investigation the effects of five different anaesthetic drugs have been examined in animals in which the rostral inhibitory influences were eliminated by decerebration. Of these procaine, when administered by itself, produces excitement in the central nervous system both in man and other species, whereas signs of stimulation of the central nervous system are difficult to obtain and are rarely seen when using pentobarbitone (Frank & Saunders, 1963). The clinical use of tribromethanol for preanaesthetic sedation and paraldehyde for sedation and hypnosis in psychiatric states, characterized by excitement (Goodman & Gilman, 1965), would indicate that these drugs have little tendency to produce excitement of the central nervous system. The use of chloralose is, however, restricted to experimental animals in which it is desired to have good reflex activity in an anaesthetized animal; animals anaesthetized with this drug generally show gross movements and are very sensitive to stimulation while apparently unconscious.

All of these drugs abolished the inhibition produced by reticular stimulation at doses lower than those required to block the segmental reflex potentials and at doses much lower than those required to block the facilitation of the segmental reflex potentials, produced by stimulation of reticular formation at the same site with a higher intensity. In fact, without the anaesthetics the inhibitory effects of reticular stimulation at the sites chosen predominate and only as this inhibition is suppressed does the facilitation become manifest. We would suggest that this selective depression of powerful central inhibitory pathways is the basis for the excitement stage of general anaesthesia.

Although, thus far, we have investigated a rather limited number of anaesthetic drugs, the two most prone to produce central nervous system excitement (procaine and chloralose) abolished the reticular inhibition at doses which either potentiated (procaine) or did not significantly depress (chloralose) the size of the monosynaptic potentials. The dose required to abolish the reticular inhibition with the other drugs also markedly depressed the monosynaptic reflex potential. This depression of the monosynaptic potential was greatest with pentobarbitone and least with tribromethanol. This was the one consistent difference in the pattern of effects produced by these two groups of anaesthetic drugs and is probably related to the difference in the propensity of these two groups of drugs to produce signs of central nervous excitement.

This investigation was supported by Medical Research Council of Canada.

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(*Received October*, 12 1970)