J. Physiol. (1972), **223**, *pp.* 803–814
With 7 text-figures
Printed in Great Britain

THE EFFECTS OF ANAESTHETICS ON SYNAPTIC EXCITATION AND INHIBITION IN THE OLFACTORY BULB

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(*Received 7 February 1972*)

SUMMARY

1. The effects of anaesthetics (pentobarbitone, hexobarbitone, halothane, urethane, chloralose, chloral hydrate and ethanol) on the extracellular field potentials of the olfactory bulb produced by lateral olfactory tract stimulation were analysed.

2. Relatively large doses of all the anaesthetics (e.g. pentobarbitone, 40–70 mg/kg) depressed the synaptic excitation of granule cells.

3. The antidromic invasion of mitral cell dendrites was only slightly less sensitive to the anaesthetics than was the synaptic excitation of granule cells.

4. A wide dose range of anaesthetics (e.g. pentobarbitone, 3–60 mg/kg) prolonged the granule cell post-synaptic inhibition of mitral cells. All the anaesthetics, except ethanol, prolonged the inhibition.

5. The action of anaesthetics on post-synaptic inhibition was due to a specific effect on the inhibitory synapses.

6. Amino-oxyacetic acid, an inhibitor of GABA catabolism, had little effect on the synaptic inhibition or on the ability of hexobarbital to prolong the inhibition. This suggests that the prolongation seen with anaesthetics is not a result of interfering with GABA catabolism.

7. The present results are compared with results obtained with anaesthetics in other areas of the nervous system and it is proposed that prolongation of 'gaba-ergic' inhibition might contribute to an agent's ability to produce general anaesthesia.

INTRODUCTION

Numerous neurophysiological studies have been conducted in an attempt to localize a site of action for anaesthetic agents. These studies, principally on the spinal nervous pathways, have shown that synaptic

transmission is more vulnerable to anaesthetics than is axonal conduction (Brooks & Eccles, 1947; Rall, 1955; Somjen, 1963, 1967; Somjen & Gill, 1963) and that small doses of barbiturates reduce the amount of transmitter released by the monosynaptic excitatory afferents to motoneurones (Løyning, Oshima, Yokota, 1964; Weakly, 1969). In contrast other studies have shown that a wide variety of anaesthetics can markedly prolong spinal presynaptic inhibition (Eccles & Malcolm, 1946; Eccles, Schmidt & Willis, 1963; Schmidt, 1963; Miyahara, Esplin & Zablocka, 1966; Besson, Abdelmoumene, Alenard & Conseiller, 1968) which is thought to involve GABA (Eccles *et al.* 1963; Curtis, Duggan, Felix & Johnston, 1971; Barker & Nicoll, 1972).

These studies on the spinal cord may not fully explain the cellular site of action of anaesthesia since it is not known whether similar actions also prevail at cortical and subcortical sites, thought to be more sensitive to anaesthetics. Furthermore, effects of anaesthetics on post-synaptic inhibition have rarely been analysed. Thus a cortical pathway in which both synaptic excitation and inhibition could be analysed simultaneously would be a great advantage in studying the action of anaesthetics. The dendrodendritic inhibitory pathway in the olfactory bulb offers such a preparation. Recently, it has been reported that pentobarbitone can prolong such inhibition (Westecker, 1971).

METHODS

New Zealand white rabbits (1·5–2·0 kg) were anaesthetized with halothane, tracheotomized, placed in a rabbit head holder, and surgically decerebrated at the mid-collicular level with a spatula which was inserted just subtentorially. Some degree of swelling of the olfactory bulb often occurred following the decerebration and a number of procedures were tried in an attempt to reduce this problem, even though results obtained from such animals did not differ from those obtained from animals in which there was no detectable swelling. Care was taken to avoid disrupting the cerebral aqueduct during the decerebration. In some animals the ventricles were exposed by removing the overlying parietal cortex, thus allowing the c.s.f. to escape. In some animals a metal plate was inserted into the frontal lobes to separate the olfactory bulbs from the rest of the brain (Nicoll, 1969). Anaesthesia was discontinued following decerebration.

The lateral olfactory tract (LOT) (the main efferent pathway from the olfactory bulbs) was stimulated with a bipolar concentric electrode which was placed stereotaxically on the LOT. Field potentials were recorded in the olfactory bulb with a low resistance glass micropipette (1–2 M-NaCl) and displayed on a 565 Tektronics oscilloscope. Responses were obtained from the external plexiform layer (EPL) and care was taken to maintain the recording electrode at a position which gave the maximum field potential (approximately 100–150 μ peripheral to the mitral cell layer). The location of the micro-electrode tip was determined by the characteristic field potential produced by LOT stimulation (Phillips, Powell & Shepherd, 1963). Serial depth recordings of the field potentials before and after anaesthesia indicated

that the position in the EPL from which the largest field potential could be recorded did not shift after anaesthesia. Responses were usually obtained from the EPL on the ventral side because recording conditions proved more stable on this side. When large doses of anaesthetics were used, the animals were paralysed with I.V. Flaxidel (gallamine triethiodide) and artificially respirated. This should rule out indirect secondary effects of anaesthetics caused by respiratory depression. Rectal temperature was maintained at 37–39° C with a heating pad.

Anaesthetics employed included pentobarbitone (Diamond Labs., ten animals), hexobarbitone (Winthrop Labs., sixteen animals), chloral hydrate (Merck and Co., three animals), chloralose (Sigma Labs, six animals), urethane (Sigma Labs., two animals), halothane (Ayerst Labs., five animals), and ethanol (five animals). All agents were given intravenously except halothane which was vaporized in a Fluotex with 100% O_2 and inhaled through the tracheal cannula in an 'open circuit'. At least 45 min were allowed to elapse following the administration of a short acting anaesthetic before another agent was given. In initial experiments this proved to be an adequate time for complete recovery. Post-synaptic inhibition and the action of hexobarbitone on such inhibition were examined before and after (five experiments) the S.C. administration of the inhibitor of GABA catabolism, amino-oxyacetic acid hemihydrochloride (AOAA) (K and K and Sigma Laboratories).

The pathway which has been studied in the present series of experiments can be summarized as follows. The mitral cells, which form a thin layer in the olfactory bulb, are the major relay neurones and their axons form the LOT. Dendritic processes of mitral cells extend into the EPL and make contacts with the processes of granule cells. Electronmicroscopic studies (Andres, 1965; Rall, Shepherd, Reese & Brightman, 1966; Price & Powell, 1970) have shown that these contacts consist of reciprocal synapses in which one synapse of the pair is oriented from mitral dendrite to granule cell process while the other is oriented from the granule process back on to the mitral dendrite. There is considerable physiological evidence based on the analysis of extracellular field potentials that the synapses oriented from mitral to granule cell process are excitatory while the synapses from granule to mitral dendrites are inhibitory (Rall *et al.* 1966; Rall & Shepherd, 1968; Nicoll, 1969; Westeker, 1971).

RESULTS

Action of anaesthetics on antidromic invasion and synaptic excitation. Stimulation of the LOT elicits an extracellular field potential in the external plexiform layer composed of two negative waves (Figs. 1*A*, 2). It is now generally agreed that the first negative wave corresponds to the antidromic invasion of mitral cells and their dendrites, while the second negative wave reflects the synaptic excitation of granule cell processes by the mitral cell dendrites (see Methods for a description of this pathway). In the unanaesthetized preparation there are often small all-or-none unitary potentials superimposed on the antidromic field potential (Fig. 1*B*, top trace). Furthermore, there were usually two components to the second negative wave; an early sharp negativity followed by a longer lasting negativity (see arrows in Figs. 1*A*, 2*A*). Except for smoothing out the inflexion between these two components (Fig. 1*A*) and suppressing the small unitary potentials on the antidromic field (Fig. 1*B*), the anaesthetics

employed had little effect on antidromic invasion or synaptic excitation until relatively large doses were reached. Synaptic excitation of granule cells was only slightly more sensitive to anaesthetics than was dendritic invasion of mitral cells and as the dose of anaesthetic was increased both responses were attenuated in an almost parallel fashion (Fig. 2*A–D*). If the size of the synaptic potential and the antidromic potential are expressed as a ratio, the differential effect can be seen more clearly. For instance, for chloralose (Fig. 2*D*) the ratio in the control is 3·76 and

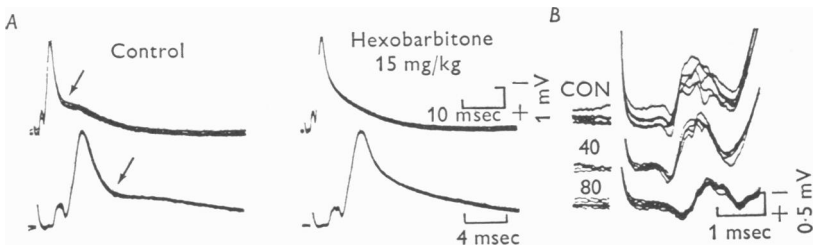

Fig. 1. Action of moderate doses of anaesthetics on antidromic invasion and synaptic excitation. In *A* hexobarbitone, 15 mg/kg, smoothes out the inflexion on the potential resulting from the synaptic excitation of granule cells (shown at two sweep speeds). *B* shows small all-or-none potentials superimposed on the mitral dendrite antidromic field and the sensitivity of these potentials to chloralose. Upper record is control response (CON). Dose of chloralose expressed in mg/kg at left of each trace. Each record in this and following Figures is composed of 5–20 superimposed traces.

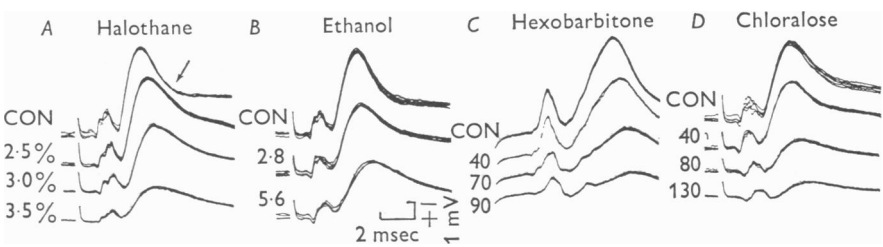

Fig. 2. Action of increasing doses of anaesthetics on antidromic invasion and synaptic excitation. *A*, upper record in this and following records is control (CON). Dose of halothane is expressed as percentage in oxygen. The ratios of the height of the synaptic potential and the height of the antidromic potential in these traces is as follows: CON = 3·33, 2·5% = 3·33, 3·0% = 3·2, 3·5% = 2·7. *B*, dose of ethanol is expressed in g/kg. Results are from same animal as *A*. Ratios are as follows: CON = 3·33, 2·8 g/kg = 3·33 and 5·6 g/kg = 2·9. *C*, dose of hexobarbitone in mg/kg. Ratios are as follows: CON = 2·2, 40 mg/kg = 2·0, 70 mg/kg = 2·0, 90 mg/kg = 1·33. *D*, dose of chloralose in mg/kg. Top three traces in this series were enlarged in Fig. 1*B*. Voltage and time scale (given at bottom of *B*) is the same for all records.

progressively decreases (40 mg/kg – 3·2, 80 mg/kg – 2·4, 130 mg/kg – 1·3) as the dose is increased. To ensure that this was a true reduction in synaptic excitation, a series of responses to increasing stimulus strengths to the LOT was obtained before and after administering anaesthetics (Fig. 3*A*). Fig. 3*B* shows that the ratio (size of synaptic potential divided by size of antidromic potential) is reduced at all stimulus strengths following doses of pentobarbitone, 40 and 70 mg/kg.

Action of anaesthetics on synaptic inhibition. The extent and duration of the granule cell inhibition of mitral cells (see Methods for description of the pathway) can be assessed by pairing stimuli to the LOT and recording the size of the field potential elicited by the second LOT stimulus. By superimposing sweeps at different stimulus intervals a profile of the inhibition can be obtained rapidly (e.g. Fig. 4*A*). Such an analysis of

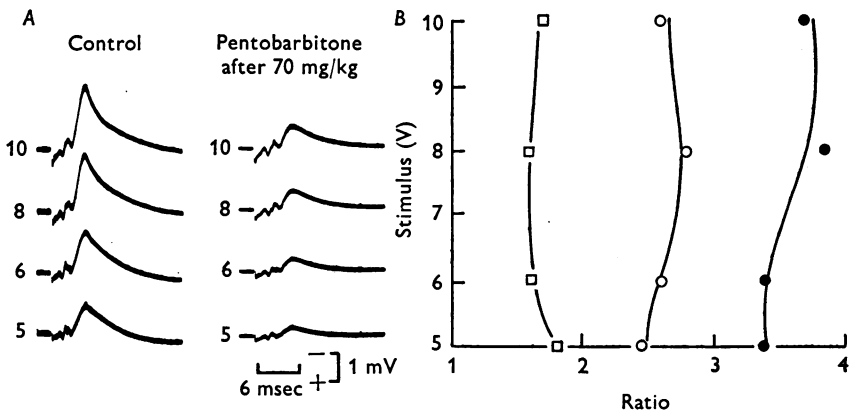

Fig. 3. Action of pentobarbitone on the excitation of granule cells. A series of responses to increasing stimulus strengths to the LOT before (series at left) and after pentobarbitone 70 mg/kg I.V. (series at right). Voltage and time scale is the same for all traces. *B*, the ratios of the size of the synaptic and antidromic potentials (abscissa) before (filled circles) and after pentobarbitone, 40 mg/kg (open circles) and 70 mg/kg (squares) are plotted against the size of the LOT stimulus (ordinate).

granule cell inhibition reveals that extremely small doses of anaesthetics (e.g. pentobarbitone, 3 mg/kg) prolong the inhibition. Fig. 4 shows the effect of increasing doses of pentobarbitone on granule cell inhibition. Prolongation of the inhibition occurs at doses of pentobarbitone that have no effect (30 mg/kg) or a depressant effect (50 mg/kg) on the excitation of the granule cells. The duration of inhibition increases with increasing doses (50 mg/kg) until large doses are reached at which point the inhibition is reduced (70 mg/kg). Presumably this reduction with large doses, which was seen with a number of the anaesthetics (e.g. chloralose, Fig. 5*A*), is due in large part to the depression of the excitatory limb of the pathway.

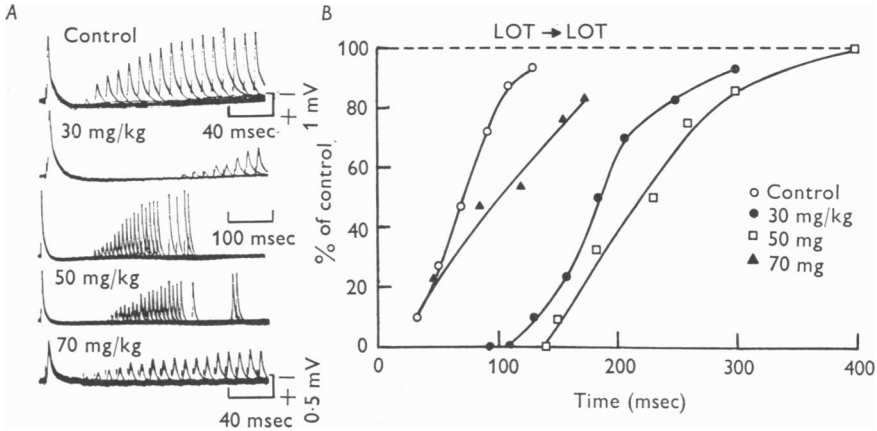

Fig. 4. Effect of pentobarbitone on granule cell inhibition as tested by pairing LOT stimuli. *A*, top trace is control. Second record is after pentobarbitone 30 mg/kg. Third record is at a slower sweep speed. Fourth trace is after a total dose of 50 mg/kg and bottom trace is after an accumulative dose of 70 mg/kg. Note different calibration in bottom record. In *B* the size of the test response (expressed as the percent of control) is plotted against time (expressed as the time between the conditioning and test LOT stimulus).

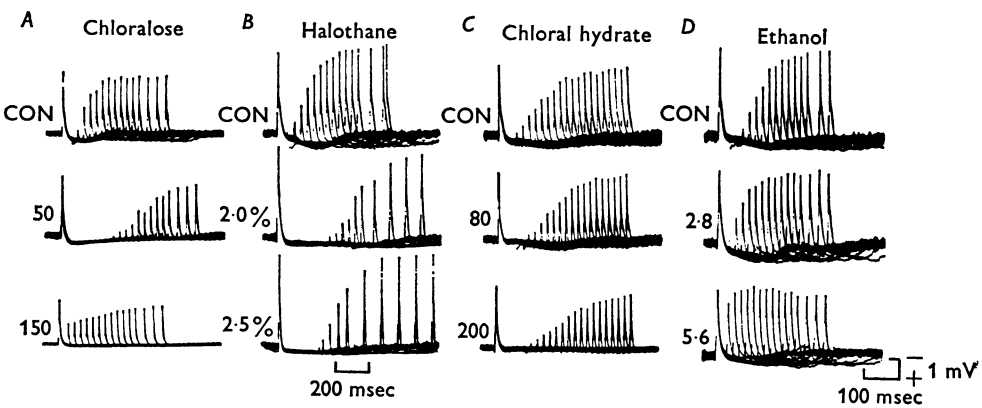

Fig. 5. Effect of anaesthetics on granule cell inhibition as tested by pairing LOT stimuli. The top record is the control (CON) for each series. Dose of chloralose and chloral hydrate is expressed in mg/kg. Dose of halothane is given in percentage in oxygen and that of ethanol in g/kg. Results with ethanol are from same experiment as records in Fig. 2*B*. The calibration at the lower right-hand corner applies to all records except the bottom record in column *B* which is at half the sweep speed.

Small doses of chloral hydrate, halothane, hexobarbitone, and urethane also prolonged the granule cell inhibition (Fig. 5*B*, *C*). However, ethanol appeared to be an exception as only antagonisms of the inhibition was seen at all dose levels (Fig. 5*D*).

Another way of analysing the effect of anaesthetics on granule cell inhibition is to observe the P-wave which follows the synaptic excitation of granule cells (Nicoll, 1969; Nicoll, 1972). This wave is in part the current source of the granule cell inhibition. While the anaesthetics often reduced the amplitude of the P-wave, they all, except for ethanol, caused a marked prolongation of this wave (Fig. 6*A–D*) and the duration of the inhibition, as tested by pairing stimuli to the LOT, paralleled the prolongation of the P-wave. For instance, for chloralose (Fig. 6*A*) the duration of the P-wave increased from 130 to approximately 350 msec, while the inhibition of a test LOT stimulus in this experiment (not illustrated) increased from 150 to 400 msec.

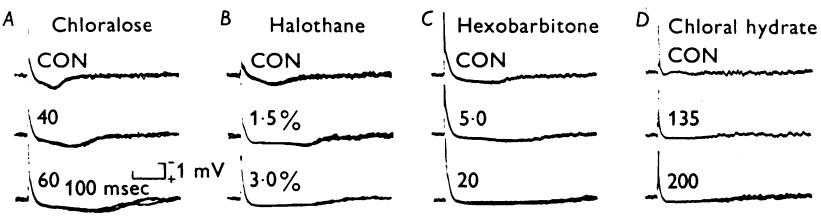

Fig. 6. Effect of anaesthetics on the duration of the P-wave. Doses of chloralose, hexobarbitone, and chloral hydrate are given in mg/kg. Dose of halothane is given as percent in oxygen. Calibration in all records is the same.

Action of amino-oxyacetic acid on synaptic inhibition. One possible mechanism by which anaesthetics might prolong synaptic inhibition is by preventing the enzymatic break-down of the inhibitory transmitter (Eccles, 1964). There is now considerable pharmacological evidence that GABA is the transmitter released from granule cells (Nicoll, 1970; Felix & McLennan, 1971; McLennan, 1971; Nicoll, 1971). To test the possibility that the anaesthetics might be acting by inhibiting the metabolism of GABA, the action of an inhibitor of GABA metabolism, amino-oxyacetic acid (AOAA), has been analysed in five experiments. It was found that doses of this agent (40 mg/kg) which are known markedly to inhibit GABA metabolism (Wallach, 1961) had little effect on the duration of granule cell inhibition observed up to 4½ hr after the injection of AOAA (Fig. 7, records on left). Furthermore, AOAA had no effect on the ability of hexobarbitone to prolong the inhibition (Fig. 7, records on right), at any time up to 4½ hr after the injection of AOAA.

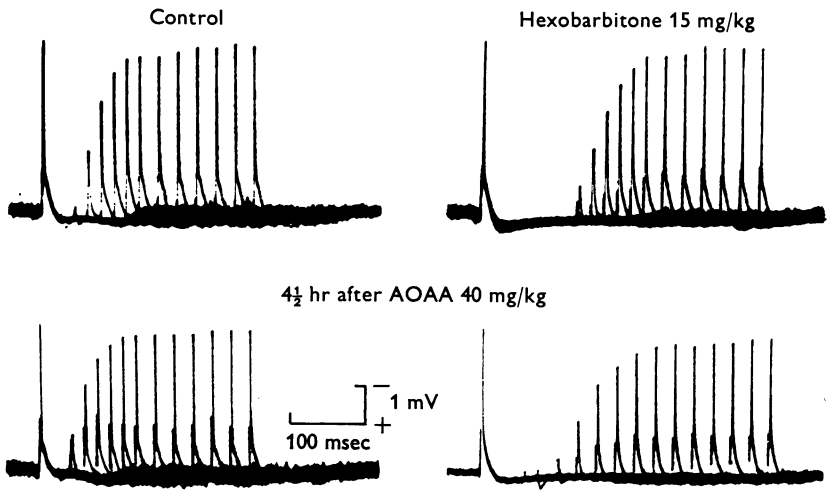

Fig. 7. Effect of AOAA on granule cell inhibition and on the prolongation of inhibition by hexobarbitone. Record at upper left is control. Record at right was obtained just after an injection of hexobarbitone 15 mg/kg. Record at lower left was obtained 4½ hr after the administration of AOAA 40 mg/kg s.c. Record at right was taken just after the injection of hexobarbitone 15 mg/kg.

DISCUSSION

The depressant effect of anaesthetics on the synaptic excitation of granule cells in the olfactory bulb is similar to their effect in the spinal cord (Brooks & Eccles, 1947; Rall, 1955; Somjen, 1963, 1967; Somjen & Gill, 1963; Løyning *et al.* 1964; Shapovalou, 1964; Weakly, 1964), sympathetic ganglion (Larrabee & Posternak, 1952; Matthews & Quilliam, 1964), neuromuscular junction (Thesleff, 1956), and the olfactory cortex (Richards, 1971) and is consistent with the hypothesis that barbiturates (and a number of other structurally unrelated anaesthetics) reduce the amount of transmitter liberated at excitatory synapses. However, relatively large doses of anaesthetic, usually above the dose considered necessary to induce general anaesthesia of the animal, were required to demonstrate these effects and furthermore the antidromic invasion of mitral cell dendrites showed a sensitivity to anaesthetics similar to that of synaptic excitation.

The depression and delay in antidromic invasion of mitral cells seen in the present experiments (Figs. 1*B*, 2*A–D*) are similar to the effect of barbiturates on antidromic invasion of Purkinje cell dendrites (Eccles, Faber & Táboříková, 1971). The small unitary potentials seen in the antidromic field presumably arise from the dendrites of mitral cells since

they are recorded approximately 150μ from the soma. These potentials, which were depressed by anaesthetics, suggest that the dendrites of mitral cells may be capable of supporting action potentials.

The potentiating effect of anaesthetics on granule cell inhibition was quite striking; this phenomenon, unlike that of depression of synaptic excitation, could be demonstrated with extremely small doses and it was present over a very wide dose range of anaesthetics. Indeed, the degree of potentiation of granule cell inhibition seen with various doses of a particular anaesthetic roughly correlates with the degree of general anaesthesia produced. For example, with pentobarbitone the potentiation is greatest in the anaesthetic dose range for this agent in rabbits (30–60 mg/kg) (Stewart & Stolman, 1960). Furthermore, this effect was seen with all anaesthetics tested, except ethanol. The prolongation appeared to be a specific action of the anaesthetic on the inhibitory synapse as it could be demonstrated with doses which either had no effect or had a depressant effect on the antidromic invasion of mitral cells and the synaptic excitation of granule cells.

There are few studies concerning the effect of anaesthetics on post-synaptic inhibition. Weakly, Esplin & Zablocka (1967) were unable to detect a specific potentiation of the direct inhibition of motoneurones by barbiturates, but the direct effect of barbiturates on the monosynaptic reflex was a complicating factor. A potentiation of synaptic inhibition with hexobarbitone has been reported for the recurrent inhibition of motoneurones (Larson & Major, 1970) and the effect appears to be due to an action on the inhibitory synapse. The effect of barbiturates on the interaction of parallel fibre excitation and basket cell inhibition in cerebellar Purkinje cells has been studied (Bloedal & Roberts, 1969; Eccles *et al.* 1971) and the apparent enhancement of basket cell inhibition seen after the administration of barbiturate was ascribed to a reduction in parallel fibre excitation (Eccles *et al.* 1971). However, it seems reasonable that these results could be due, in part, to a direct potentiation of the basket cell inhibition.

In contrast to the paucity of studies on the action of anaesthetics on post-synaptic inhibition, a number of studies have been done on pre-synaptic inhibition, and a variety of anaesthetics have been shown to prolong this form of inhibition (Eccles & Malcolm, 1946; Eccles *et al.* 1963; Schmidt, 1963; Miyahara *et al.* 1966; Besson *et al.* 1968), which is thought to be mediated by GABA (Eccles *et al.* 1963; Curtis *et al.* 1971; Barker & Nicoll, 1972). The present results in the olfactory bulb are thus of particular interest as GABA appears to be the post-synaptic inhibitory transmitter in this system (Nicoll, 1970; Felix & McLennan, 1971; McLennan, 1971; Nicoll. 1971).

Recent developments in neuropharmacology (cf. Krnjević, 1970; Curtis & Felix, 1971) emphasize the apparent ubiquity of 'gaba-ergic' inhibition in supraspinal pathways. It seems reasonable that the prolongation of inhibition seen in the present experiments may be applicable at other 'gaba-ergic' synapses and that this in turn might contribute to an agent's ability to produce general anaesthesia.

One possible mechanism by which anaesthetics might prolong inhibition is by preventing the catabolism of GABA. Cortical inhibition, which is thought to be mediated by GABA (Krnjević, 1970; Curtis & Felix, 1971), has been reported to be prolonged following the blockage of GABA metabolism with AOAA (Kelly, Renault & Gottesfeld, 1971). In the present experiments AOAA had little effect on the synaptic inhibition or on the ability of hexobarbitone to prolong the inhibition. This suggests that the prolongation seen here with anaesthetics is not a result of interfering with GABA metabolism. Other mechanisms which should be considered are: a blockage of the reuptake process for the inhibitory transmitter, an enhancement of the post-synaptic action of the inhibitory transmitter, and a facilitation of the excitation–secretion coupling mechanism for the inhibitory transmitter. These possibilities are under current evaluation.

I thank Dr F. E. Bloom for his criticism of the manuscript.

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