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THE ACTION OF CARBON DIOXIDE ON AFFERENT TRANSMISSION IN THE DORSAL COLUMN–LEMNISCAL SYSTEM

BY MARY E. MORRIS

From the Department of Research in Anaesthesia, McGill University, Montreal, Canada

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SUMMARY

1. Transmission in the lemniscal afferent pathway was studied in thirteen decerebrate, unanaesthetized cats while changing the concentration of inspired P_{CO_2}.

2. 2–20% CO_2, when inhaled for $\leqslant$ 10 min, raised the mean tissue P_{CO_2}, recorded from the surface of the medulla or cerebellum, from 22 torr to between 26 and 93 torr.

3. Medial lemniscal potentials were evoked by stimulation of a forelimb nerve and recorded from the transected surface of the contralateral mid-brain. The transmission of supramaximal responses was progressively and reversibly depressed as tissue levels of P_{CO_2} were raised and lowered. The time course of the changes in transmission corresponded closely to changes in the tissue P_{CO_2}.

4. The amplitude of the main early lemniscal peak was decreased to 80% by the inhalation of 20% CO_2. A late component of the lemniscal response, presumably due to repetitive firing and conduction in smaller fibres and polysynaptic pathways, was more affected than the early main response.

5. The failure of transmission was unrelated to threshold changes in the peripheral nerve, since potentials recorded close to the site of stimulation showed no changes.

6. Increases in the transmission time of the main lemniscal potentials were uniform and $< 10\%$ during the administration of CO_2 and did not appear to contribute to amplitude changes.

7. The inhibition of afferent transmission from one nerve by a preceding conditioning volley in a second nerve was not altered by hypercarbia.

8. It is concluded that CO_2 has a blocking action on afferent transmission in the pre-thalamic lemniscal system. The site of this block may be

at the synapses and/or other regions of low safety factor in the afferent fibres.

INTRODUCTION

Carbon dioxide, when inspired in sufficient quantities by animals and man, has a narcotic action (Hickman, 1824; Brown, 1930; Waters, 1937). During this narcosis the electrocorticogram is diffusely desynchronized and reduced in amplitude (Gellhorn, 1952; Friedlander & Hill, 1954). Cortical activation from somatic inputs has been shown to increase with low concentrations of CO_2 and to decrease with higher anaesthetic concentrations, while afferent impulses in special sensory projections were only progressively dampened (Gellhorn, 1952, 1953). The narcosis has been attributed to a suppression of arousal mechanisms by depression of reticular formation activity (Bremer & Thomas, 1936; Gellhorn, 1953; Dell & Bonvallet, 1954). However, alterations in sensory transmission will certainly influence central excitatory states, even though loss of perception and the conscious state may not be explained simply by the removal of afferent impulses.

Sensory discrimination, tested in studies of visual, auditory and cutaneous thermal threshold, is decreased by the inhalation of moderate concentrations of CO_2 (7–10%) (Gellhorn & Spiesman, 1935*a*, *b*; Gellhorn, 1936; Stokes, Chapman & Smith, 1948). The excitability of cortical neurones is directly depressed by CO_2 (Krnjević, Randić & Siesjö, 1965). There are both excitatory and depressant effects of CO_2 on some sensory fibres (Boistel & Coraboeuf, 1954; Coroboeuf, 1954), but vertebrate nerves are mainly depressed with both a reduction of excitability and block of conduction (Gruenhagen, 1872; Szpilman & Luchsinger, 1881; Davis, Pascual & Rice, 1928; Lehmann, 1937; Hettwer, 1938; Lorente de Nó, 1947). Studies of the action of CO_2 on synaptic transmission have been limited to the motoneurone arc, where there is a depressant effect (Brooks & Eccles, 1947; Washizu, 1960) which is selectively greater on monosynaptic than polysynaptic reflexes (Kirstein, 1951; Esplin & Rosenstein, 1963). Although it is known that the excitability of the motoneurones is decreased by CO_2 (Washizu, 1960; Gill & Kuno, 1963), the site of action of CO_2 in synaptic regions has not yet been defined.

Therefore, in order to understand the effects of CO_2 on both sensory and synaptic mechanisms, studies have been made on transmission in the dorsal column nuclei where the primary afferent fibres make their first synapses; the relay fibres of the nuclei form the main contribution to the medial lemniscus (Ranson & Ingram, 1932; Busch, 1961).

The present experiments examine in the decerebrate cat the effects of brief changes in the concentration of inspired P_{CO_2} on the overall trans-

mission of impulses from stimulation of forelimb nerves to the medial lemniscal fibres. In addition, the interaction of afferent transmission from different nerves is studied during administrations of CO_2. Levels of the brain tissue P_{CO_2}, continuously recorded at the surface, are correlated with changes in transmission. Preliminary reports of these experiments have already appeared (Morris, 1969*a*, *b*).

METHODS

Experiments were made on thirteen decerebrate cats. Anaesthesia, induced with ethyl chloride and ether and maintained with halothane and oxygen, was discontinued after the dissection; thereafter oxygen was given through a non-rebreathing system. Three animals breathed spontaneously; the others were paralysed with succinylcholine chloride (Anectine, Burroughs Wellcome & Co. Ltd, 0·1 % (w/v) in physiological saline, infused intravenously) and artificially ventilated by a Palmer respirator with tidal volumes of 20–30 ml. at a rate of 30/min. Rectal temperatures were maintained between 36–37° C by a servo-controlled heating pad on which the animals lay.

Surgical preparation. The trachea was cannulated and the common carotid arteries were ligated. Catheters were placed in a femoral artery and vein, for the monitoring of blood pressure and administration of fluids.

The superficial radial cutaneous and median nerves at the wrist of one forelimb were dissected free from surrounding tissue for a distance of 2–3 cm and ligated and sectioned. The nerves were then mounted on bipolar platinum electrodes and coated with a mixture of Vaseline and mineral oil. They remained exposed to room temperature.

After a wide, bilateral craniotomy a decerebration was made at the intercollicular level, by sliding a blunt spatula along the edge of the bony tentorium and removing the cerebral hemispheres. Blood loss during this procedure was minimized and compensated for, if necessary, by (i) ligation of the carotid arteries, (ii) elevation of the head, (iii) increasing the depth of anaesthesia, so as to lower the blood pressure, (iv) the application of oxidized cellulose (Surgicel, Johnson & Johnson) to severed vessels, (v) the intravenous injection of a plasma expander (Subtosan, Poulenc Ltd).

In all but two experiments, the dorsal surface of the medulla was exposed by laminectomy of the first and second cervical vertebrae and resection of part of the occipital bone overlying the cerebellum. After the dura was opened the brain was kept moist by a thin polythylene cover or a continuous flow of warm mammalian Ringer solution. A 1 cm-square chlorided silver plate was sutured between muscles of the back of the neck, for use as an electrical ground.

Stimulation and recording. Square pulses of 0·01–0·20 msec duration, at 0·5 or 1 Hz were delivered to the forelimb nerves.

Monophasic potentials were recorded differentially from the transected surface of the mid-brain with two insulated platinum electrodes of 0·3 mm diameter, which were positioned separately. One electrode was first placed approximately according to co-ordinates from Jasper & Ajmone-Marsan (1954), its final position being adjusted so as to record the maximal amplitude of evoked response. The indifferent electrode was at a point 7–10 mm away, where there was no response. Amplified potentials were displayed on an oscilloscope and photographed. In two experiments these potentials were integrated with respect to time by means of an analogue gating unit.

In five experiments the afferent volley was monitored by a second pair of electrodes, placed 20–30 mm proximal to the point of stimulation on the peripheral nerve.

Fig. 1 is a diagram of the stimulating (S) and recording (R) arrangements and the monosynaptic relay of the dorsal column – lemniscal pathway in the cuneate. The upper traces show an example of the lemniscal potentials and their attenuation as the frequency of stimulation was increased from 1 to 200 Hz.

Administration of CO_2. Observations were made before ($\leqslant$ 5 min), during (5–10 min), and after (20–30 min) the inhalation of CO_2. The intervals between administrations of CO_2 were approximately 30 min. In most experiments each animal was given CO_2 four times, in progressively increasing concentrations.

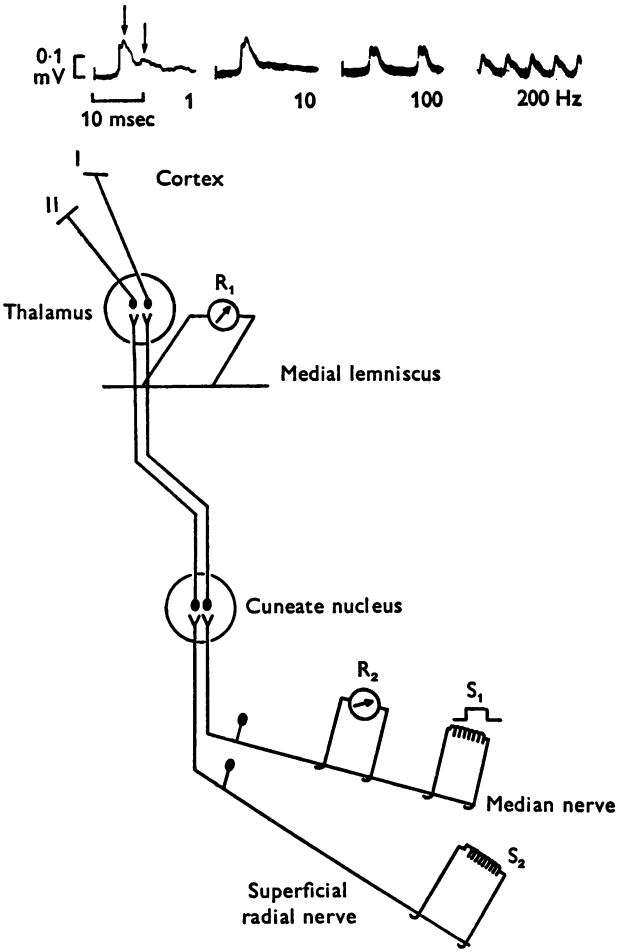

Fig. 1. Diagram of main lemniscal projection from forelimb and arrangement of stimulating and recording electrodes. S_1 and S_2, bipolar electrodes stimulating forelimb nerves. R_1, differential recording from transected lemniscal fibres. R_2, recording of afferent volley from second electrode pair, proximal to stimulating electrodes. Example of lemniscal potentials and frequency-following, during supramaximal stimulation of superficial radial nerve at 1, 10, 100 and 200 Hz for periods < 5 sec. Arrows mark early and late peaks of response.

Mixtures of approximately 2, 4, 10 and 20 % were obtained by varying the ratio of CO_2 and oxygen in a total flow of 5 l./min from a British Oxygen Company rotameter array. On one occasion the P_{CO_2} of these mixtures (ten consecutive settings at each concentration) was measured with a CO_2 electrode (Siesjö, 1961); the estimates of 2, 4, 10 and 20 % CO_2 gave, at a barometric pressure of 757 torr, measured mean values (± S.E.) of 21·4 (± 0·84), 40·2 (± 0·43), 86·2 (± 1·3) and 148 (± 2·4) torr.

Measurement of tissue P_{CO_2}. In nine experiments the mean tissue P_{CO_2} was continuously measured from the surface of the brain (Siesjö, 1961, 1965; Krnjević *et al.* 1965) from the medulla in seven cats, from the cerebellum in two cats. A miniature tissue P_{CO_2} electrode, supplied by L. Eschweiler & Co., Kiel, W. Germany, was used. It was prepared with an electrolyte solution of 0·0001 M-$NaHCO_3$ and 0·025 M-KCl and a 12 μ Teflon membrane. Its voltage output was measured with a Beckman 160 Physiological Gas Analyzer (input impedance 500 Ω), and recorded with a pen writer. The time constant of the electrode for changes of calibrating gases from 2 % to 10 % CO_2 was between 20 and 30 sec when P_{CO_2} was raised and slightly less when it was lowered. In four animals calibrations were made at the same temperature as that of the brain; in five others a temperature correction was calculated for the electrode: $\Delta \log P_{CO_2} = -0{\cdot}011\ \Delta T$. Under the best conditions there were drifts of 1–2 mV over periods up to 12 h; at other times the electrode was calibrated more frequently and the corrections assumed a constant rate of drift.

RESULTS

Effects of CO_2 on medial lemniscal responses to supramaximal stimulation

Fig. 2 shows an example of maximal medial lemniscal responses to stimulation of a forelimb nerve before, during and after the inhalation of increasing concentrations of CO_2. Similar or comparable progressive depressions of afferent transmission were observed during administrations of 2, 4, 10 and 20 % CO_2 to twelve other cats (twenty-six observations). With 2 and 4 % CO_2 there were small increases or decreases in the amplitude of potentials; 10 % CO_2 caused definite depression; and the greatest decreases were seen with 20 % CO_2. The early peak of largely monosynaptic responses (at the first arrow) was less affected than the later peak (at the second arrow), which fails at low frequencies and may arise from polysynaptic paths, the dorsal column relay or recurrent collaterals (Amassian & De Vito, 1957). Table 1 summarizes the results from all these experiments, in which the amplitude of the earliest peak of the response returned to the level of the mean control value (± 5 %) within 20 min after the withdrawal of CO_2.

The onset of the depression of transmission was within 30 sec to 1 min of the increase in inspired CO_2. As a rule the maximal effects were observed within 3–5 min and they persisted during the administration of CO_2. The recovery often began within a few minutes of the withdrawal of CO_2 and was usually complete. Occasionally it started before the withdrawal of CO_2 and sometimes was delayed or incomplete. Fig. 3 illustrates the time course and intensity of the depression of the lemniscal response during an inhalation

of 20% CO_2. The corresponding changes in the continuous tissue P_{CO_2} record are shown on the same time scale.

Changes in tissue P_{CO_2}. During the administrations of CO_2 for $\leqslant$ 10 min, the brain tissue levels of P_{CO_2}, continuously recorded in nine cats (as shown in Fig. 3), increased from control levels and approached a steady-state at raised values (Siesjö, 1965). In these decerebrate animals there was no marked difference between the tissue P_{CO_2} of the medulla or cerebellum and that known for the cortex (Pontén & Siesjö, 1966; Morris, 1970), as

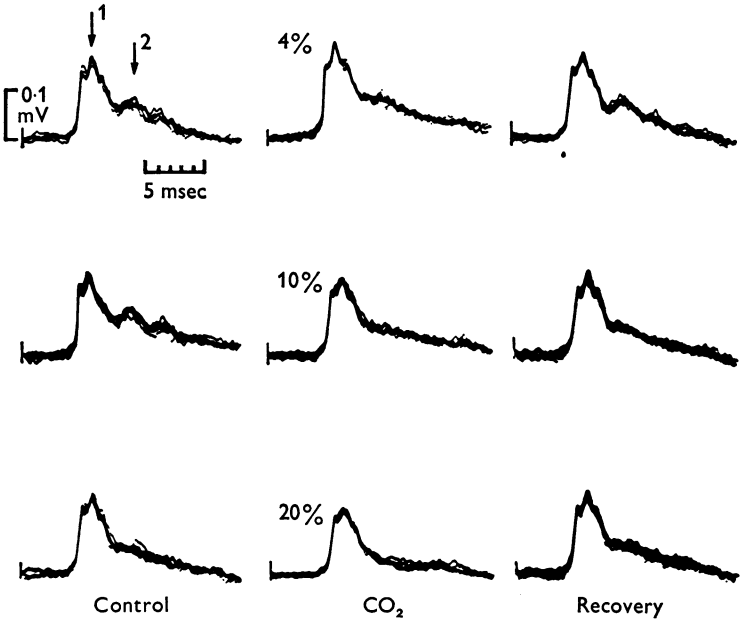

Fig. 2. Effects of inhaling 4, 10 and 20% CO_2 for 9–10 min, on medial lemniscal responses evoked by supramaximal stimulation of superficial radial nerve. Traces are 5–10 photographic superimpositions. Arrows mark early (1) and late (2) peaks of the response. Observations during spontaneous respiration.

TABLE 1. Medial lemniscal responses evoked by supramaximal stimulation of forelimb nerve during the administration of CO_2 (twenty-nine observations from thirteen cats)

	2% CO_2 (n = 8)	4% CO_2 (n = 5)	10% CO_2 (n = 8)	20% CO_2 (n = 8)
Transmission (%)*	98·06 (±4·02)†	92·16 (±6·98)	87·15 (±2·05)	80·01 (±2·12)

* Amplitude of first peak of response, expressed as % of a control mean of eight to ten observations. Values are the means of single measurements at the time of maximal depression. n = number of observations.

† S.E. of mean.

judged by the tissue and arterial P_{CO_2} values at the start of experiments. The mean tissue-arterial P_{CO_2} difference ($\pm$ S.E.) in the present experiments was $3{\cdot}25 \pm 0{\cdot}99$ torr. The control tissue P_{CO_2} measured in one spontaneously breathing cat was $29{\cdot}8 \pm 1{\cdot}9$ torr, which is consistent with the arterial P_{CO_2} values of Fink & Schoolman (1963) for awake, unrestrained cats ($28{\cdot}0 \pm 1{\cdot}2$ torr) and of Ngai (1957) for decerebrate cats ($27{\cdot}0 \pm 2{\cdot}8$ torr). For eight artificially ventilated cats the mean control tissue P_{CO_2} was somewhat

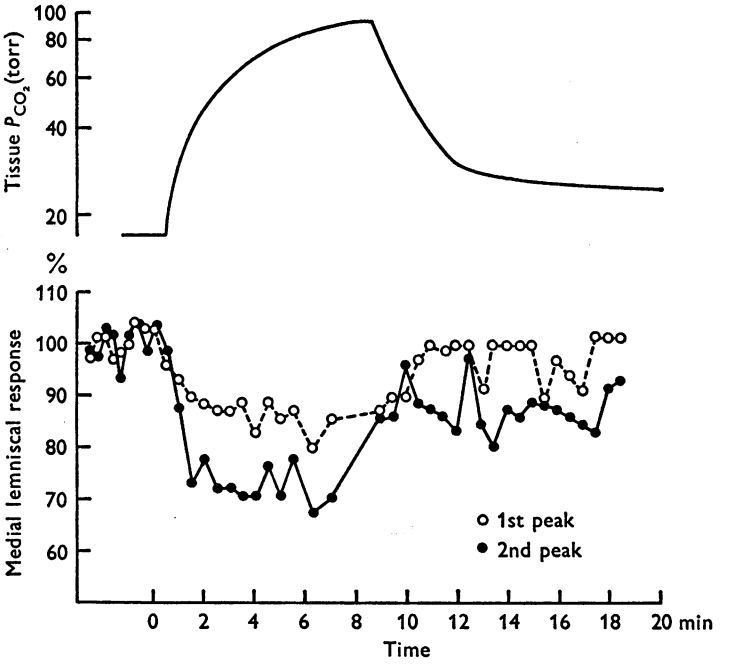

Fig. 3. Changes in brain tissue P_{CO_2} and medial lemniscal response to supramaximal stimulation of median nerve during administration of 20% CO_2 for 8 min (starting at 0 time). Responses are single measurements of potential amplitudes (expressed as % of control) of first (○) and second (●) peaks, with respective transmission times of 6 and 9 msec. Tissue P_{CO_2} returned to control level only 25 min after CO_2 inhalation stopped (note that P_{CO_2} scale is logarithmic).

lower ($20{\cdot}9 \pm 1{\cdot}5$ torr). When the inspired P_{CO_2} was raised, the tissue P_{CO_2} of the spontaneously breathing cat increased to correspondingly higher values than those of the ventilated animals.

The latency of onset of tissue P_{CO_2} changes was approximately 30–60 sec for an increase in inspired P_{CO_2} and 40–80 sec for a decrease. When the inhalation of CO_2 was stopped, the return of tissue P_{CO_2} to previous control levels was often delayed (see Fig. 3). The lag in recovery is explained partly by the electrode time constant and partly by the tissue and equipment

wash-out time, but the apparent delay is exaggerated by the logarithmic nature of the P_{CO_2} electrode response. In Table 2 the initial and maximal tissue P_{CO_2} values (mean ± S.E.) are shown for all experiments where CO_2 was measured.

Control studies. In two experiments a comparison was made of changes in the amplitude of the first peak and changes in the area under the combined first and second groups of lemniscal potentials (cf. potentials and integrals in Fig. 5). With increasing stimulus intensity, amplitudes were linearly related to area; when CO_2 was inhaled this relation persisted and there were no significant changes in slope ($P > 0{\cdot}1$). Therefore changes in the amplitude of the first peak could be assumed to be representative of changes in total transmission.

TABLE 2. Brain tissue P_{CO_2} recorded during the administration of CO_2 (twenty-three observations from nine cats). These recordings were made from the surface of the medulla in seven cats and from the surface of the cerebellum in two cats. Respiration was spontaneous in one animal and by artificial ventilation in eight animals. S.E. of mean in parentheses

	2% CO_2 ($n = 5$)	4% CO_2 ($n = 5$)	10% (CO_2) ($n = 7$)	20% CO_2 ($n = 6$)
Initial tissue P_{CO_2} (torr)	22·0(±2·98)	21·0(±2·81)	22·0(±2·22)	24·2(±3·94)
Maximum tissue P_{CO_2} (torr)	26·4(±3·12)	33·6(±2·29)	56·86(±4·44)	93·3(±5·58)
Δ Tissue P_{CO_2} (torr) (difference between maximum and initial values)	4·4(±0·68)	12·6(±2·11)	33·4(±4·56)	69·2(±3·0)
Time CO_2 inhaled (min)	8·1(±0·33)	7·3(±0·73)	9·2(±1·2)	8·3(±0·48)

In two cats (included in the grouped data of Table 1) the medulla was not exposed, in order to avoid disturbances of function caused by local surgery and a fall in temperature. In these animals the progressive depression of the transmission of maximal responses by increasing amounts of CO_2 did not differ from that in other experiments; the decreases caused by 20% CO_2 were to 81 and 83%.

The effects of CO_2 inhalation on the maximal responses of three cats, which were allowed to breathe spontaneously, resembled those of the animals which had received paralysing drugs and artificial ventilation; 20% CO_2 depressed transmission to 77 and 72% in two cats during spontaneous respiration and to between 71 and 87% in six other animals which were artificially ventilated.

Effects of CO_2 on medial lemniscal responses to submaximal stimulation

Changes at the peripheral nerve. In order to estimate changes in excitability at the site of stimulation, the effects of 2–20 % CO_2 on the afferent volley recorded at the peripheral nerve were studied in five experiments (fourteen observations). The amplitude of these potentials, evoked by both supramaximal and submaximal stimulation, was unchanged (as in Fig. 4)

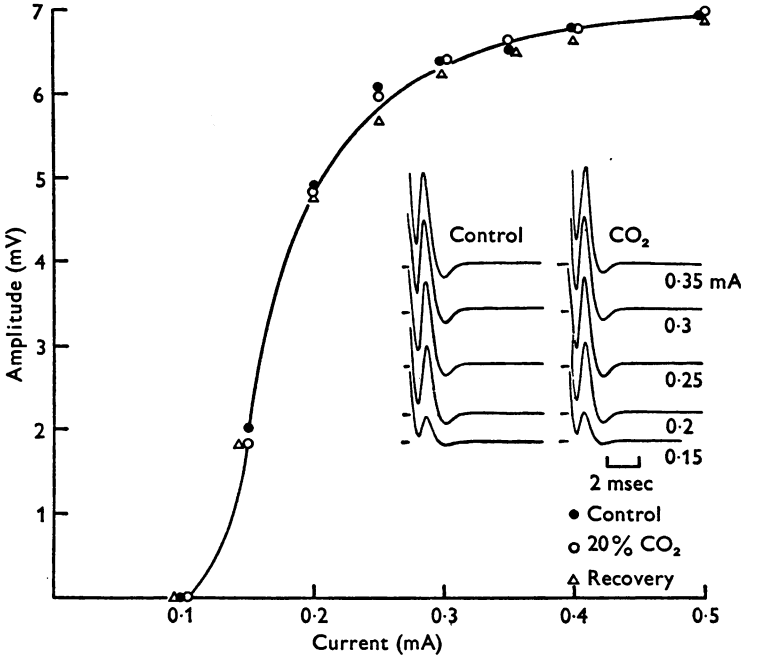

Fig. 4. Effect of 20 % CO_2 on amplitude of afferent volley potentials in the superficial radial nerve, in response to increasing intensities of stimulation at a more distal point. Symbols represent responses before (●), during (○), and after (△) CO_2 was inhaled for 5 min. Traces show actual potentials before and during CO_2.

or even increased; on two occasions decreases occurred in unparalysed animals while breathing 2 % CO_2 and were probably related to disturbance of electrode contacts.

Changes in afferent transmission. Medial lemniscal responses to all intensities of peripheral nerve stimulation were progressively depressed by the inhalation of increasing amounts of CO_2. Fig. 5 is an example of the lemniscal potentials and their time-integrals, at increasing strengths of stimulation, before, during and after the administration of 20 % CO_2; both traces show the depression of transmission which affected later responses

more than earlier ones. In Fig. 6 are graphs of the peak amplitudes from another experiment; the large decrease in delayed responses can be clearly seen. Similar effects were observed in nine other animals (twenty-five observations with 2–20 % CO_2).

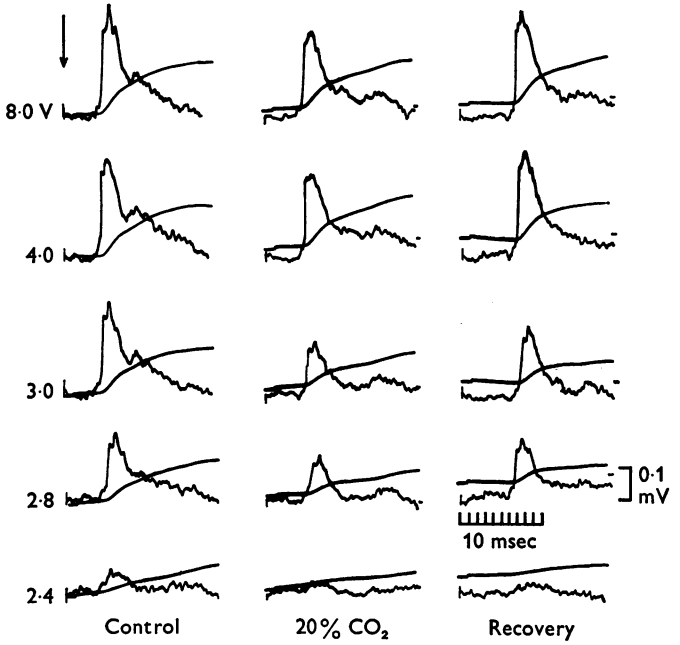

Fig. 5. Changes in medial lemniscal responses to increasing intensities of stimulation of the median nerve during an inhalation of 20 % CO_2 for 6 min which increased brain tissue P_{CO_2} from 25 to 110 torr. The second smoother trace shows the area of these potentials, after electronic integration. Arrow marks stimulus artifact. Recovery records 5 min after CO_2 administration stopped.

Correlation of tissue P_{CO_2} and depression of transmission

The changes in afferent transmission were correlated with the changing levels of the tissue P_{CO_2}: Fig. 7 illustrates the relation of the percentage depression of the amplitude of maximal lemniscal responses and the increasing brain P_{CO_2} during an inhalation of 20 % CO_2; observations were made at 30 sec intervals over a period of 8 min (data from the experiment of Fig. 3). The changes in both the first peak (open circles) and the second peak (filled circles) were significantly correlated with the tissue P_{CO_2} ($r = +0{\cdot}90$ and $+0{\cdot}87$ ($P < 0{\cdot}001$)).

Fig. 8 relates the largest changes in transmission to the peak of change in tissue P_{CO_2}, when different concentrations of CO_2 were administered to seven cats. With greater changes in tissue P_{CO_2} there was greater depres-

sion of transmission. The more marked sensitivity of submaximal responses is shown by the vertical bars connecting the changes in these responses (filled symbols) with those of their paired maximal responses (open symbols), recorded at approximately the same time in the same animal.

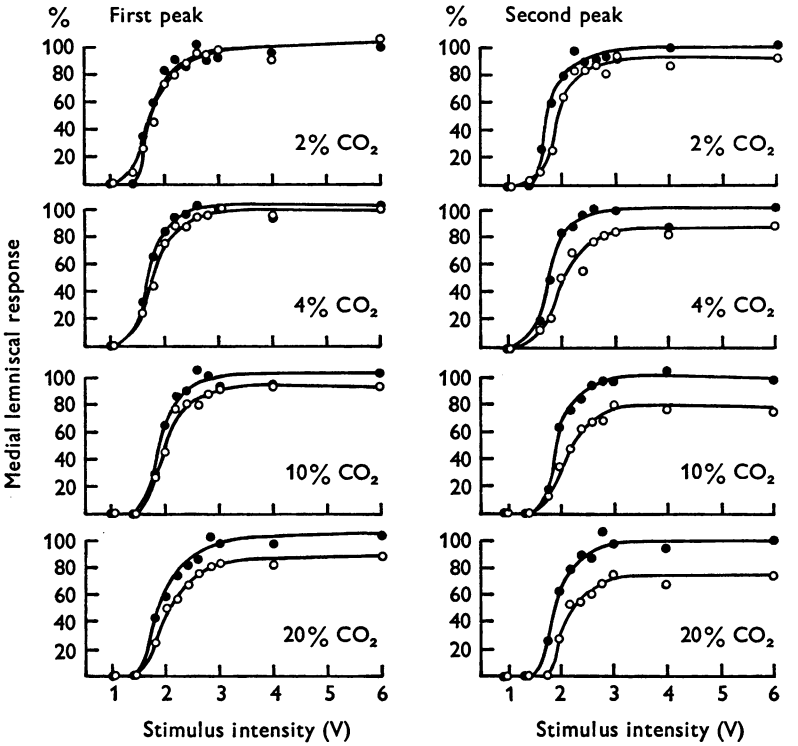

Fig. 6. Effects of 2, 4, 10 and 20 % CO_2 on amplitudes of medial lemniscal potentials, evoked at different intensities of median nerve stimulation. At left first peak, transmission time 6 msec; at right second peak, transmission time 9 msec. ●—control values; ○—while giving CO_2 (8–9 min). Measurements of single responses from one experiment; curves drawn by eye. Recovery potentials after CO_2 were near control values.

Effects of CO_2 on transmission time

The latency of transmission of impulses from a peripheral nerve to the mid-brain was prolonged by the breathing of CO_2. These effects were greater with higher concentrations of CO_2, as shown in the maximal responses of Fig. 9. The most marked delay was with 20 % CO_2, which caused the potentials to shift farther from the vertical dotted line through the control first peak. The graph of Fig. 10 shows measurements of the transmission time of the earliest peak of these potentials before and during the inhalation of 4, 10 and 20 % CO_2, at times and values indicated on the

inset traces of the tissue P_{CO_2} records. Similar changes were observed in four other animals; when 20 % CO_2 was inspired the increases in transmission time ranged from 0·4 to 0·8 msec (equivalent to changes of 4–10 %). The time for transmission of the later lemniscal peak appeared to be more prolonged than that for the early component.

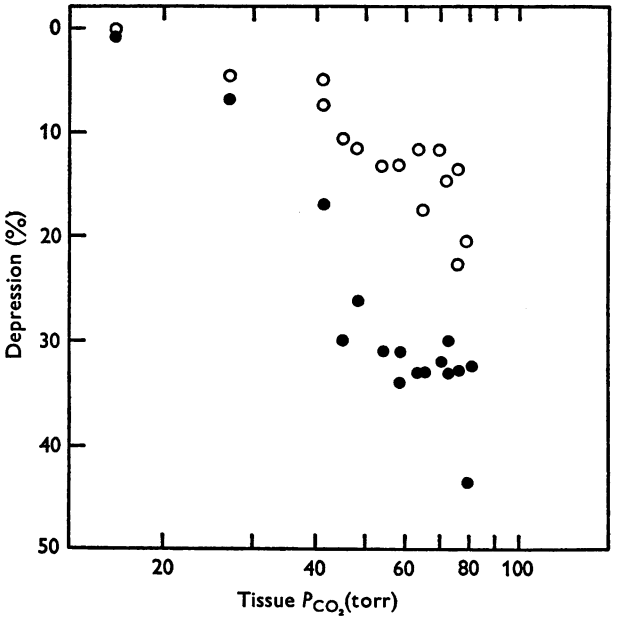

Fig. 7. Correlation of tissue P_{CO_2} and depression of medial lemniscal responses to supramaximal stimulation of median nerve before and during inhalation of 20 % CO_2 for 8 min. ○—early peak response; ●—later, smaller peak. Time course of changes for this experiment illustrated in Fig. 3 (note logarithmic scale for tissue P_{CO_2}).

The time-integration of potentials (as in Fig. 5) showed that there was a depression of the total transmission of impulses, and that amplitude changes could not be attributed solely to desynchronization. An estimate can be made of the contribution of changes in transmission time to changes in the amplitude of potentials: if, as a first approximation, the first peak of the lemniscal response is assumed to have the form of a triangle, and if its area remains constant, any changes in height will be inversely proportional to changes in the length of the base. Hence, any changes in transmission time will be reflected by corresponding changes in the amplitude. It follows therefore that the amplitude changes due to temporal dispersion during the breathing of 20 % CO_2 in these experiments would not exceed 4–10 %.

Effects of CO_2 on conditioning of medial lemniscal responses

Transmission through the cuneate is decreased by the action of a preceding volley in another nerve (Andersen, Eccles, Oshima & Schmidt, 1964). In four of the present experiments the effects of breathing CO_2 on this inhibition of lemniscal responses were observed, when the optimal test-conditioning interval was 30–40 msec and when the interval was

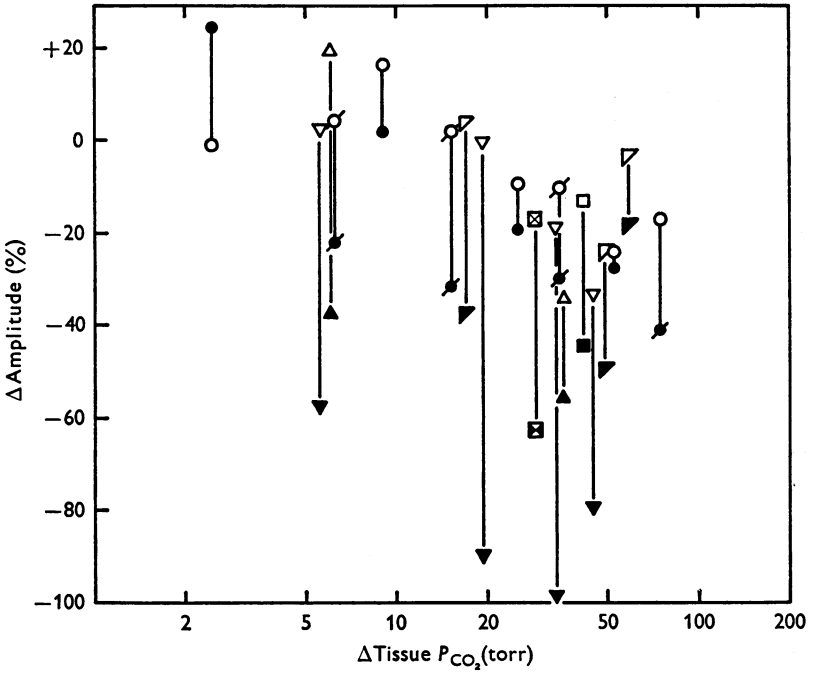

Fig. 8. Correlation of changes in brain tissue P_{CO_2} with changes in lemniscal responses to forelimb nerve stimulation during administrations of 2–20 % CO_2 in seven cats (thirty-eight observations). Amplitudes of the earliest peak potentials are expressed as % of a mean control response (n = 10). Each set of similar symbols represents responses in one cat. Open symbols: supramaximal stimulation (3–8 × voltage evoking maximal response); filled symbols: submaximal stimulation (30–60 % of voltage evoking maximal response). Vertical bars connect maximal and submaximal values recorded at short intervals during single administrations of CO_2 (note logarithmic scale for tissue P_{CO_2}).

varied between 10 and 200 msec, with supramaximal intensities of stimulation of both nerves. Both unconditioned and conditioned responses appeared to be affected to the same extent by 4–20 % CO_2 and the time course of the inhibition was not changed. This can be seen in the lower graphs in Fig. 11, which show the depression of both unconditioned and

conditioned first and second lemniscal peaks when 20 % CO_2 was given for 8 min (conditioning-test interval of 30 msec). When the conditioning-test interval was varied between 15–200 msec (see Fig. 11, middle set of graphs) 20 % CO_2 caused no remarkable changes in the degree of inhibition.

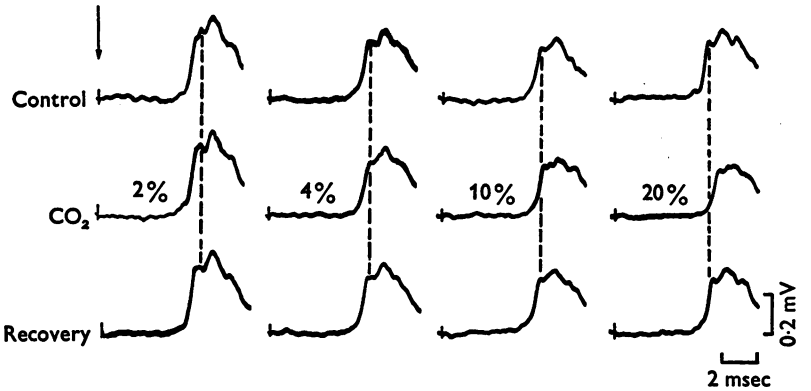

Fig. 9. Effects of 2, 4, 10 and 20 % CO_2 on transmission time of medial lemniscal responses to supramaximal stimulation of superficial radial nerve. Interrupted vertical line drawn through first peak of control responses: note progressively increasing shift of potentials to right with increasing concentrations of CO_2. Tissue P_{CO_2}, recorded at the same time from the surface of the cerebellum, increased from control levels of 14–17 torr to 19, 32, 55, and 80 torr respectively during the inhalation of 2, 4, 10 and 20 % CO_2. Data from this experiment also illustrated in Figs. 2 and 10. Estimated conduction distance 30 cm.

DISCUSSION

The over-all efficiency of transmission of impulses from the periphery to the medial lemniscus was decreased when brain tissue P_{CO_2} was raised by the inhalation of CO_2. Since transmission was depressed even when the peripheral nerve was stimulated supramaximally, and there were only minimal changes in the potentials recorded from the nerve, the depression of the lemniscal response cannot be ascribed to a reduction in the number of fibres excited at the periphery. Nor is it likely that the raised CO_2 could have caused a significant diminution in unit spike height and duration (Krnjević *et al.* 1965; Washizu, 1960). Although transmission times were increased, the changes were small; they appeared to involve all fibres to the same extent, since the shape of the early main group of potentials, representing conduction in the fastest and most homogeneous fibres, did not change significantly. Even the maximal increases in transmission time would make but a small contribution to a decrease in potential amplitude by desynchronization. The time-integral potential data provide further evidence that the changes in transmission can be attributed mainly to changes in the number of active lemniscal fibres.

All components of the lemniscal response to stimulation of a peripheral nerve were depressed by the increases of CO_2. The first lemniscal peak (latency < 8 msec) represents largely monosynaptic transmission in the dorsal column–lemniscal projection through the cuneate; there is a small contribution of rapidly conducted potentials from the indirect disynaptic

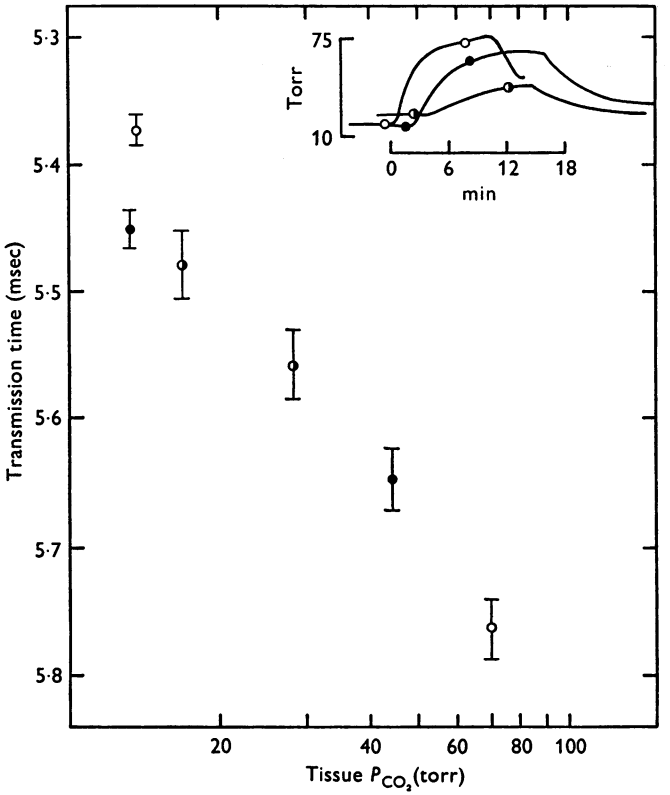

Fig. 10. Correlation between tissue P_{CO_2} and transmission time of medial lemniscal responses to supramaximal stimulation of superficial radial nerve. Data represent first peak transmission time (mean ± S.E., n = 5–9) before and during three administrations of CO_2 (◑–4 % CO_2, ●–10 % CO_2, ○–20 % CO_2) from one experiment (also shown in Figs. 2 and 8). Superimposed traces in upper right corner from tissue P_{CO_2} records, with symbols corresponding to those of graph (note: logarithmic scale for tissue P_{CO_2}).

spino-thalamic tract (Whitehorn, Morse & Towe, 1969; L. Fedina, G. Gordon & A. Lundberg, unpublished observations, quoted by Andersen, Etholm & Gordon, 1970), which arises from fibres ascending in the postero-lateral column to the lateral cervical nucleus (Morin, 1955; Brodal & Rexed, 1953). The depression of afferent lemniscal transmission by CO_2 may therefore involve both the dorsal column and spino-cervical paths.

Although some of the late lemniscal responses might be in polysynaptic paths (e.g. the spino-thalamic) they are most likely to be due to repetitive firing of the cuneo-thalamic neurones, arising from the relay of the reflex activity presumed to be generated in the branching regions of the afferent

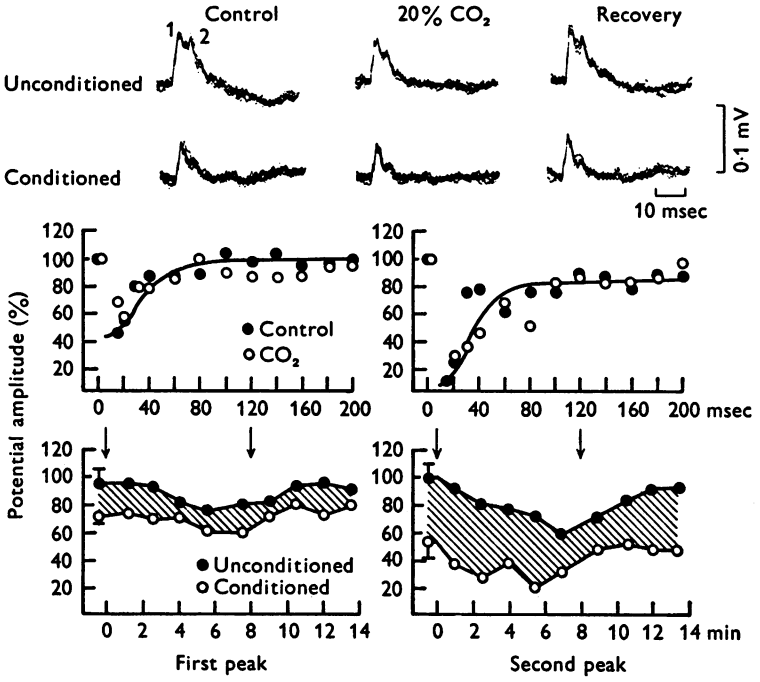

Fig. 11. Effects of 20% CO_2 on conditioning of afferent transmission to medial lemniscus from superficial radial nerve by a preceding volley in median nerve. Supramaximal stimulation of both nerves. Traces at top show responses (unconditioned and conditioned at 30 msec interval), before, during (7 min), and after (10 min) CO_2. The lowermost graphs show amplitude changes of the first and second potential peaks (marked,1 2 in traces). Responses expressed as % of mean control (vertical bar = S.D., n = 10): ●–unconditioned, ○–conditioned, with volley interval 30 msec. Arrows mark times of CO_2 administration. Shading shows degree of inhibition caused by conditioning (symbols after control are means of two to three responses over 1–1·5 min). Upper graphs show conditioned responses (first and second peak amplitudes expressed as % of unconditioned responses) when test-conditioning volley intervals varied between 15–200 msec. ●–control, ○–after 20% CO_2 inhaled for 7 min.

fibres and known as the dorsal column and dorsal root reflexes (Toennies, 1939; Amassian & De Vito, 1957; Andersen, Eccles, Schmidt & Yokota, 1964). The greater sensitivity of the late firing may be partly explained by a greater temporal dispersal, but it may also be related to a lower security

of transmission, reflected in the inability to follow high frequencies of stimulation.

The greater depressant action of CO_2 on submaximal than on maximal lemniscal potentials may be due to non-linear input–output characteristics of the pathway when near-maximal stimuli are applied. Furthermore, alteration of synaptic output by selective effects on excitatory and inhibitory mechanisms (Andersen, Eccles, Oshima & Schmidt, 1964), such as sparing or potentiation of inhibition, might explain the observed changes in transmission. However, the lack of clear-cut effects of CO_2 on afferent volley interactions in the present experiments suggests that excitatory and inhibitory inputs are depressed to the same degree.

The block of conduction caused by CO_2 could take place at points of low safety factor, such as in the region of the synapses (Brooks & Eccles, 1947) or where the afferent fibres enter the spinal cord and branch (Wall, Lettvin, McCulloch & Pitts, 1955; Raymond, 1969). Synaptic efficiency might be decreased or inputs could be blocked before their arrival at the synapses. In the paper which follows (Morris, 1971), these possibilities were tested by micro-electrode stimulation in the cuneate. Both pre- and post-synaptic excitability were found to be depressed by CO_2 but the efficiency of synaptic transfer was well maintained. Therefore the failure of transmission in this pathway appears to be due mainly to a block of conduction in the primary afferent fibres.

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