The Influence of Cerebellum on Carbon Dioxide Responses in the Dog

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Abstract The influence of the cerebellum on the baseline ventilatory responses while breathing oxygen and O₂-CO₂ mixture was investigated in mongrel dogs anaesthetized with sodium pentobarbital. Ablation of the anterior lobe of the cerebellum significantly depressed both the baseline and CO₂ responses. By contrast, the posterior lobe ablation did not produce any significant change. The results indicate that the anterior lobe of the cerebellum may exert a facilitatory effect on respiration. The exact nature of the underlying mechanism is not known, but the anterior lobe of the cerebellum may directly or indirectly modulate the activity of the vagal afferents.

Key words: carbon dioxide response, cerebellum, control of respiration, hypercapnia.

The main function of the cerebellum is coordination of voluntary movement. It is also known to influence respiration. For instance, ablation of the whole or part of the cerebellum is known to significantly alter the breathing pattern, the responsiveness to chemical drive, and the central and reflex excitability of the different respiratory motoneurone pools (CORDA *et al.*, 1966; DECIMA and VON EULER, 1969; SPECK and WEBBER, 1982). Electrical stimulation (LUTHERER and WILLIAMS, 1986) or electrolytic lesions (WILLIAMS *et al.*, 1989) of fastigial nucleus of the cerebellum can alter respiration. Both inhibitory (STELLA, 1939; MORUZZI, 1940) as well as facilitatory effects of the cerebellum on respiration have been observed (PANDA *et al.*, 1979). STELLA (1939) showed that ablation of the cerebellum in decerebrate dogs produced an increase in the rate and depth of respiration. On the other hand, PANDA *et al.* (1979) observed that mechanical stimulation of muscle receptors produced a stimulatory effect on respiration which was considerably reduced after cooling or ablation of the anterior lobe of the cerebellum.

The present study was planned to investigate the influence of the cerebellum on respiratory response to carbon dioxide inhalation.

MATERIALS AND METHODS

Experiments were performed on twenty mongrel dogs, each weighing 8–10 kg, anaesthetized with 35 mg/kg sodium pentobarbital (Sagatal, May & Baker, U.K.) administered intraperitoneally. Additional doses were given by i.v. to maintain a steady level of light anaesthesia. The trachea was cannulated (see Fig. 1) so that the animal breathed through a pneumotachograph (Fleish No. 1) attached to a wide bore tube through which flowed humidified respiratory gas(es), viz. pure oxygen or O_2 - CO_2 mixture. The flow rate of the gas was maintained at approximately five times the expected minute ventilation under the experimental conditions. Thus, rebreathing of expired air was largely prevented and the respiratory measurements were made under hyperoxic conditions to eliminate the complicating effects of peripheral chemoreceptors. The tracheal air flow rates through the pneumotachograph were recorded as differential pressure across the pneumotachograph with a Statham PM 97 strain gauge. The flow signals were integrated by Beckman type 9826 integrating coupler to give a continuous record of tidal volume (V_T). Thus, inspiratory and expiratory flow rates, V_T and frequency of breathing (f_B) were recorded on an 8-channel type R Beckman Dynograph. Minute ventilation (V_E) was computed by multiplying f_B and V_T (mean of all breaths recorded over 1 min). The animal breathed successively—for 5 min each—oxygen, 4% CO_2 in oxygen, and 6% CO_2 in oxygen. During the 5th minute of breathing, inspiratory and expiratory flow rates, V_T and f_B were recorded. Simultaneously, arterial blood was drawn over the middle 30 s and analysed for P_{O_2} , P_{CO_2} and pH with BMS 3 MK micro-electrode system (Radiometer, Copenhagen, Denmark).

Fig. 1. Shows the breathing set-up used in the experiment. Tracheal cannula is connected to pneumotachograph (P) with PM97 differential pressure gauge. The animal breathes humidified gas(es) from the wide bore tube.

Rectal temperature was monitored with a mercury thermometer and maintained at 37–38°C throughout the experiment.

In two groups of 10 dogs each, these observations (respiratory parameters while breathing O₂ or O₂-CO₂) were repeated after ablation of the anterior (Group I) or posterior lobe of the cerebellum (Group II) respectively by a method described earlier (PANDA *et al.*, 1979). Following the surgery, at least 30 min were allowed for recovery.

The statistical analysis of the data was done using Student's *t*-test for paired values (SNEDECOR and COCHRAN, 1980) to determine the difference in the carbon dioxide respiratory responses between the intact and post-cerebellectomy states. *p* values of less than 0.05 were considered significant.

RESULTS

Group I

In this group of 10 dogs, while breathing high concentration of oxygen, the mean $\pm$ S.E. resting respiratory parameters were: P_{aCO_2} 38.51 ± 1.36 Torr; minute ventilation ($\dot{V}_E$) 2.99 ± 0.21 l; frequency of breathing (f_B) 16.22 ± 2.2 /min; tidal volume (V_T) 0.202 ± 0.18 l. Inhalation of 4 and 6% CO₂ in oxygen produced the expected significant increase in all these parameters (Table 1 and Fig. 2). It can be seen from the Table that after ablation of the anterior lobe of cerebellum the ventilation responses were significantly decreased to oxygen as well as O₂-CO₂ breathing. The baseline f_B was reduced by 4 breaths/min, P_{aCO_2} rose by 3 Torr, $\dot{V}_E$ fell by 0.59 l/min. However, there was a marginal increase in V_T . When the P_{aCO_2} was increased after CO₂ breathing under hyperoxic conditions, although the f_B , $\dot{V}_E$, and V_T increased, the slope of the $\dot{V}_E/P_{aCO_2}$ was significantly shifted to the right and the apnoea point was increased by 3 Torr from the intact cerebellum value. The f_B response to CO₂ breathing was significantly depressed ($p < 0.05$) after ablation of the anterior lobe of cerebellum while the V_T response did not show any significant change.

Group II

In this group of 10 dogs the posterior lobe of the cerebellum was ablated. In contrast with Group I, the ablation did not produce any significant difference in the basal (breathing high concentration of oxygen) respiratory parameters (V_T , f_B , and $\dot{V}_E$). The pre-ablation (control) $\dot{V}_E/P_{aCO_2}$ curve also did not differ significantly from that in Group I. Furthermore, there was no significant difference in the control and post-ablation $\dot{V}_E/P_{aCO_2}$ response curves (Table 1 and Fig. 2).

The mean control intra-arterial pressure in all experiments was 94.6 ± 2 Torr with no significant change after cerebellar ablation.

Table 1. Ventilatory responses to carbon dioxide breathing in dogs with intact brain and after ablation of the anterior or posterior lobe of the cerebellum.

Group I—10 dogs						Group II—10 dogs					
Brain intact			Anterior lobe ablation			Brain intact			Posterior lobe ablation		
Mean P_{aCO_2} (Torr)	Mean $\dot{V}_E$ (l)		Mean P_{aCO_2} (Torr)	Mean $\dot{V}_E$ (l)	P	Mean P_{aCO_2} (Torr)	Mean $\dot{V}_E$ (l)		Mean P_{aCO_2} (Torr)	Mean $\dot{V}_E$ (l)	P
38.35 ±1.36	2.99 ±0.21		41.27 ±1.45	2.4 ±0.14	<0.05	36.5 ±1.170	2.79 ±0.109		35.8 ±1.397	2.81 ±0.173	>0.05
47.14 ±2.17	5.11 ±0.269		49.32 ±2.18	3.89 ±0.34	<0.05	44.4 ±1.645	4.92 ±0.328		44.3 ±1.236	5.16 ±0.369	>0.05
57.83 ±1.7	8.09 ±0.512		58.98 ±2.05	6.02 ±0.787	<0.05	57.4 ±0.949	9.33 ±0.847		55.7 ±1.40	9.20 ±7.51	>0.05

$N=10$. All values are expressed as mean ± S.E.

Fig. 2. Effects of P_{aCO_2} on tidal volume (V_T) and respiratory frequency in two groups of dogs. In Group I (10 dogs) following control observations with intact brain (●) the anterior lobe of the cerebellum was ablated (○) and in Group II (10 dogs) following control observations with intact brain (▲), the posterior lobe of the cerebellum was removed (△). The values are means of the data and vertical bars are $\pm$ S.E.

DISCUSSION

The present study clearly demonstrates a facilitatory influence of anterior lobe of cerebellum on respiration in dogs. By contrast, the posterior cerebellar lobe did not have any effect. Thus, while ablation of the anterior lobe of cerebellum significantly depressed ventilation both under normocapnic as well as hypercapnic conditions, the posterior lobe ablation was without any effect. It may be noted that all experiments were conducted under intact vagus and hyperoxic conditions. The latter prevented any complicating respiratory effects of carotid bodies. The exact nature of the underlying mechanisms, however, have not been elucidated.

In literature, conflicting reports are available. In an earlier study from this laboratory (PANDA *et al.*, 1979), the ventilatory response to muscle receptor stimulation was reduced by ablation or cooling of the anterior lobe of the cerebellum

which also indicated a facilitatory effect of the cerebellum on respiration. On the other hand, in decerebrate dogs STELLA (1939) observed that respiratory excitation to inhalation of air containing 5 to 10% carbon dioxide was increased as much as one half times after decerebellation. The chemoreceptor reflexes were actually released from some kind of tonic inhibition. This assigns an inhibitory role to the cerebellum. MORUZZI (1940) also found an inhibitory effect of the paleocerebellar cortex (anterior lobe) on the respiration in cats.

We observed that after ablation or cooling of the anterior lobe of the cerebellum there was about 20% increase in the ventilation, but this returned to control value at the end of 5 min. Therefore, it is possible that Stella's observations on response to carbon dioxide were made soon after ablation. Our CO_2 response observations were made 30 min after ablation (when ventilation and P_{CO_2} had come back to steady levels). It is noteworthy that MANFIELD and TYUKODY (1936) also reported marked depression of respiratory response to carbon dioxide following removal of cerebellum, but information regarding blood P_{O_2} , P_{CO_2} , pH, and blood pressure was lacking. A change in the above parameters will alter the response. In the present study, the CO_2 was administered in oxygen so that P_{aO_2} remained above 500 Torr and the pH was within normal limits. The blood pressure and heart rate were continuously monitored and did not show any appreciable change from control i.e. before and after ablation of the anterior lobe.

It can be argued that the post ablation change in the carbon dioxide response curve was the nonspecific effect of trauma in the brain. This, however, is unlikely as the carbon dioxide response curve after ablation of the posterior lobe did not differ significantly from the pre-ablation values. Moreover, the experiments were conducted when the respiration, blood pressure, and reflexes had returned to steady levels after cerebellar ablation. The findings of the present study suggest that the anterior lobe of cerebellum normally exerts some facilitatory effect on respiration. Since the nature of the cerebellar control on respiration is not clear, it may be concerned with the integration of cardiovascular and respiratory changes associated with muscle contraction and coordination during exercise.

It is noteworthy that the respiratory effects of anterior cerebellum closely resemble that of vagal afferents in that its ablation depresses ventilation under normocapnic as well as hypercapnic conditions. Ventilatory responses to CO_2 breathing were depressed after vagotomy in animals and bilateral vagal block in conscious man mainly through abolition or diminution of tachypnoea (SCOTT, 1908; GUZ *et al.*, 1966; RICHARDSON and WIDDICOMBE, 1969; WEIMER and KIWULL, 1972). CLARK and VON EULER (1972) had proposed that an increase in depth of breathing with CO_2 inhalation, resulting from the stimulation of the central and peripheral chemoreceptors, increased the amount of inspiratory discharge in pulmonary stretch receptors; this terminated inspiration earlier with each deeper breath when a central threshold for the "Hering-Breuer" inflation reflex was exceeded. In this way respiratory frequency increases and the effect of vagotomy is explained. It has also been shown that the activity of the pulmonary stretch

receptors in mammals is reduced during hypercapnia produced by inhalation of CO₂ (MUSTAFA and PURVES, 1972; SANT'AMBROGIO *et al.*, 1974; BRADLEY *et al.*, 1976; COLERIDGE *et al.*, 1978). This would cause increase in f_b and change in the magnitude of V_T . In the present study this occurred on inhalation of CO₂ with intact brain and intact vagi. These responses were, however, depressed after ablation of the anterior cerebellum while leaving the vagi intact. This is unlikely to be the effect of CO₂ on pulmonary stretch receptors. It is possible that the anterior lobe of the cerebellum modulates in some way the brain stem mechanisms regulating respiration. This has been postulated by SPECK and WEBBER (1982).

The findings of the present study indicate that the anterior lobe of cerebellum may exert some influence on the brain stem mechanisms, the nature and pathways of which are not clear at present.

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