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Aminophylline enhances ventilation in phrenicotomized rats

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ABSTRACT: The aim was to test the effects of aminophylline (AP) on breathing of phrenicotomized rats. Fifty seven male rats of the Wistar strain were anaesthetized with 1.3 g·kg⁻¹ urethane i.p. They were phrenicotomized, divided into 6 groups and given 5, 10, 20, 40 and 80 mg·kg⁻¹ AP i.v. or a corresponding volume of saline. Ventilation, tracheal occlusion pressure and arterial blood gases were measured. In all animals phrenicotomy resulted in hypoventilation with corresponding hypoxaemia (from control 11.9±1.0 to 10.4±0.8 kPa) and hypercapnia (from control 4.6±0.5 to 5.5±0.6 kPa). In the control group (with saline) 4 h later the Pa_{O_2} was 8.6±1.1 kPa and Pa_{CO_2} 7.2±0.6 kPa. After AP 1 h after phrenicotomy the minute ventilation increased in a dose-dependent manner by 1–66%. 4 h after phrenicotomy the minute ventilation of rats with 20 and 40 mg·kg⁻¹ of AP was significantly higher than that of the control group. AP prevented hypoventilation when injected into phrenicotomized rats. The results give no unequivocal basis from which to decide the proportion of central and peripheral effects of AP.

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Aminophylline (AP) stimulates breathing (in addition to effects on other systems of the body) [1–3]. Apart from the well known central effects on breathing, stimulation of the contractility of respiratory muscles has been described [4, 5]. The effect of AP is supposed to be even more pronounced in fatigued respiratory muscles [6]. However, only the diaphragm has been tested for AP effects so far. Therefore, we decided to examine the effects of AP on inspiratory muscles after phrenicotomy in rats [7]. It can be assumed that the muscles which are responsible for inspiration after phrenicotomy are overloaded and may become fatigued. Respiratory muscle fatigue results in alveolar hypoventilation [8]. AP could thus prevent the hypoventilation which occurs in phrenicotomized rats [9].

Methods

We used 57 male rats of the Wistar strain with a body weight 260–320 g. They were anaesthetized with 1.3 g·kg⁻¹ urethane i.p. A tracheal tube was inserted through a tracheostomy at the level of the 4–5 tracheal ring. Arterial and venous catheters were introduced into the carotid artery and jugular vein, respectively. The body temperature was monitored with a thermistor in the colon and maintained with an infrared radiator at a level between 35–38°C. Phrenicotomy was performed bilaterally in the cervical region, as described in detail elsewhere [7].

Breathing was measured with a miniature pneumotachometer attached to the tracheal tube and a corresponding differential pressure transducer (Hewlett-Packard 270). The resulting electric signal proportional to airflow was displayed on an oscilloscope screen (Tesla OPD 602) and further integrated to provide a signal proportional to tidal volume. Both signals were recorded on a Hewlett-Packard recorder with a recording speed of 10 mm·s⁻¹. A T-piece in the tracheal tube enabled measurement of tracheal pressure through a water-filled tube connected to a pressure transducer (Hewlett-Packard 267 BC). To measure maximal inspiratory pressure, the tracheal tube was occluded for three breaths when the breathing reached the level of functional residual capacity and the pressure was recorded on the Hewlett-Packard recorder. Arterial blood samples (100 µl) were withdrawn anaerobically from the carotid artery into heparinized capillary tubes for analysis of partial pressures of oxygen and carbon dioxide on a Radiometer analyser (PHM 72). The measured values were corrected for actual body temperature of the rat.

Experimental protocol

The animals were divided in a random order into six groups. At the beginning of the experiment the animals were followed for 20 min to obtain control values. Then the phrenicotomy was performed and the blood gases and ventilation were measured again. Immediately

Table 1. – Indices of respiration after phrenicotomy.

AP	CO	PX	1 h	2 h	3 h	4 h
Breathing frequency min^{-1}						
0 mg	108	88	84	78*	72*	69*
	(13)	(9)	(7)	(6)	(7)	(7)
5 mg	108	91	91	85	79*	76*
	(13)	(8)	(9)	(6)	(6)	(7)
10 mg	109	90	104*+	100*+	92*	83
	(14)	(10)	(11)	(14)	(15)	(20)
20 mg	111	93	106*+	110*+	107*+	99+
	(19)	(13)	(15)	(15)	(15)	(23)
40 mg	110	89	106*+	101+	90	80
	(19)	(15)	(18)	(19)	(27)	(32)
80 mg	107	90	100*+	83	61*	43*+
	(10)	(6)	(11)	(10)	(12)	(10)
Tidal volume ml						
0 mg	1.79	1.61	1.52	1.49*	1.41*	1.31*
	(0.17)	(0.14)	(0.14)	(0.15)	(0.15)	(0.15)
5 mg	1.76	1.54	1.59	1.55	1.48	1.42*
	(0.13)	(0.14)	(0.22)	(0.21)	(0.19)	(0.14)
10 mg	1.73	1.52	1.67	1.57	1.53	1.45
	(0.23)	(0.13)	(0.24)	(0.17)	(0.21)	(0.25)
20 mg	1.73	1.53	1.75*	1.72*	1.69+	1.69+
	(0.23)	(0.13)	(0.24)	(0.17)	(0.17)	(0.25)
40 mg	1.72	1.54	2.01*+	2.01*+	1.81*+	1.71+
	(0.23)	(0.16)	(0.19)	(0.19)	(0.23)	(0.29)
80 mg	1.83	1.61	2.41*+	2.21*+	2.01*+	1.66+
	(0.25)	(0.25)	(0.22)	(0.29)	(0.33)	(0.32)
Minute ventilation ml·min^{-1}						
0 mg	193	141	128	116*	101*	90*
	(21)	(18)	(14)	(11)	(13)	(12)
5 mg	190	140	145	132	117*	108*
	(16)	(13)	(20)	(24)	(25)	(21)
10 mg	189	137	174*+	157*	140	120
	(21)	(18)	(20)	(25)	(30)	(30)
20 mg	193	142	186*+	189*+	181*+	167+
	(17)	(15)	(24)	(22)	(22)	(33)
40 mg	189	138	212*+	202*+	163+	136+
	(17)	(15)	(16)	(34)	(53)	(58)
80 mg	196	145	240*+	183*+	122	71*
	(22)	(23)	(39)	(43)	(38)	(24)
Occlusion pressure kPa						
0 mg	1.6	1.8	2.1*	2.1*	1.9	1.8
	(0.8)	(0.6)	(0.7)	(0.6)	(0.6)	(0.5)
5 mg	1.8	1.9	2.1*	2.2*	2.1	1.9
	(0.5)	(0.6)	(0.5)	(0.5)	(0.5)	(0.6)
10 mg	1.6	1.8	2.1*	2.2*	2.2*	2.1
	(0.3)	(0.4)	(0.4)	(0.4)	(0.5)	(0.5)
20 mg	1.6	1.7	2.2*	2.3*	2.4*	2.3*
	(0.3)	(0.4)	(0.3)	(0.3)	(0.4)	(0.4)
40 mg	1.6	1.8	2.6*	2.7*+	2.6*	2.4*
	(0.3)	(0.4)	(0.4)	(0.4)	(0.6)	(0.7)
80 mg	1.5	1.7	2.7*+	2.6*	2.1*	1.5
	(0.5)	(0.5)	(0.3)	(0.6)	(0.4)	(0.4)
Arterial carbon dioxide partial pressure kPa						
0 mg	4.58	5.50	5.86	6.26*	6.70*	7.19*

AP	CO	PX	1 h	2 h	3 h	4 h
	(0.45)	(0.41)	(0.41)	(0.41)	(0.54)	(0.61)
5 mg	4.68	5.50	5.39	6.01	6.41*	6.79*
	(0.59)	(0.81)	(0.90)	(0.65)	(0.59)	(0.69)
10 mg	4.72	5.63	4.89*+	5.20+	5.90	6.30
	(0.61)	(0.82)	(0.82)	(0.97)	(0.99)	(0.97)
20 mg	4.57	5.41	4.69*+	4.56*+	4.62*+	4.84*+
	(0.35)	(0.29)	(0.29)	(0.37)	(0.41)	(0.49)
40 mg	4.72	5.59	4.42*+	4.41*+	4.86*+	5.61+
	(0.41)	(0.51)	(0.55)	(0.63)	(1.03)	(1.27)
80 mg	4.50	5.33	4.13*+	4.66*+	5.87	7.72*
	(0.62)	(0.71)	(0.78)	(0.94)	(1.50)	(0.41)
Arterial oxygen partial pressure kPa						
0 mg	12.1	10.4	9.85	9.32*	9.05*	8.65*
	(1.05)	(0.81)	(0.94)	(0.95)	(0.99)	(1.07)
5 mg	11.9	10.5	10.3	9.86	9.38*	9.01*
	(0.62)	(0.65)	(0.82)	(1.03)	(0.99)	(0.98)
10 mg	11.8	10.2	10.1	10.0	9.86	9.58
	(1.01)	(1.07)	(1.47)	(1.07)	(1.13)	(1.07)
20 mg	11.9	10.5	10.3	10.4	10.3	10.0
	(1.17)	(0.67)	(1.47)	(1.47)	(1.51)	(1.21)
40 mg	11.9	10.7	10.2	10.2	9.98	9.62*
	(1.05)	(0.83)	(1.03)	(1.39)	(1.39)	(1.44)
80 mg	11.7	10.2	10.5	10.4	9.32	8.52*
	(0.99)	(0.63)	(0.67)	(1.31)	(0.99)	(0.87)
Duration of inspiration s						
0 mg	0.22	0.25	0.25	0.26	0.27*	0.28*
	(0.02)	(0.02)	(0.02)	(0.02)	(0.03)	(0.03)
5 mg	0.22	0.25	0.24	0.25	0.25	0.27*
	(0.03)	(0.04)	(0.03)	(0.03)	(0.03)	(0.03)
10 mg	0.23	0.26	0.22*	0.23*	0.24	0.25
	(0.03)	(0.02)	(0.02)	(0.02)	(0.03)	(0.03)
20 mg	0.22	0.25	0.21*+	0.21*+	0.22*+	0.22+
	(0.03)	(0.03)	(0.02)	(0.02)	(0.03)	(0.04)
40 mg	0.22	0.25	0.21*+	0.21*+	0.22*+	0.22+
	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)	(0.03)
80 mg	0.23	0.25	0.22*	0.23*	0.24	0.25
	(0.03)	(0.03)	(0.02)	(0.02)	(0.02)	(0.01)
Duration of expiration s						
0 mg	0.35	0.44	0.46	0.51*	0.56*	0.61*
	(0.06)	(0.07)	(0.06)	(0.05)	(0.06)	(0.07)
5 mg	0.34	0.42	0.42	0.46	0.51*	0.53*
	(0.04)	(0.05)	(0.05)	(0.05)	(0.05)	(0.06)
10 mg	0.33	0.42	0.36	0.37	0.41	0.47
	(0.05)	(0.09)	(0.06)	(0.07)	(0.07)	(0.08)
20 mg	0.33	0.41	0.35*	0.33*+	0.34*+	0.41
	(0.06)	(0.08)	(0.05)	(0.06)	(0.06)	(0.12)
40 mg	0.34	0.43	0.35*	0.41	0.48	0.56
	(0.06)	(0.08)	(0.06)	(0.08)	(0.14)	(0.17)
80 mg	0.34	0.43	0.41	0.53	0.79*	1.18*+
	(0.03)	(0.05)	(0.05)	(0.14)	(0.19)	(0.24)

Means and standard deviations (in parentheses) are given. CO: control measurement before phrenicotomy; PX: measurement immediately after phrenicotomy; 1–4 h: measurements 1–4 h after phrenicotomy; 5–80 mg: doses of aminophylline (AP) in $mg \cdot kg^{-1}$ i.v. given immediately after phrenicotomy; 0 mg: control group without AP. *: $p<0.05$ for mean value compared with value after phrenicotomy; +: $p<0.05$ for mean value compared with the value of the control group.

afterwards AP was given to rats of five groups in i.v. doses of 5, 10, 20, 40 and 80 mg·kg^{-1} respectively, during 5 min. The sixth group received 0.15 M NaCl solution in a volume of 1 ml·kg^{-1} i.v. Blood gases and ventilation were evaluated each hour after the administration of AP up to 4 h. At this time (4 h after AP administration) the sixth group of rats, which had received only saline, was given AP in a dose of 20 mg·kg^{-1}. Blood gases and ventilation were measured 1 h after the injection.

Analysis of results

To obtain values of ventilation, an average of ten breaths was used. From the record the tidal volume and the durations of inspiration, expiration and of the cycle were measured. The mean inspiratory air flow was calculated as the ratio of tidal volume to inspiratory duration. The inspiratory duty cycle was calculated as the ratio of inspiratory duration to cycle duration. Minute ventilation was calculated as the product of tidal volume and frequency of breathing. The maximal inspiratory efforts during tracheal occlusion were read from the tracheal pressure record. The results were evaluated statistically using analysis of variance and Student's t-test, as appropriate.

Results

The rats after phrenicotomy invariably decreased minute ventilation and, consequently, also alveolar ventilation, as evidenced by the increase of $Paco_2$ and decrease of Pao_2 (table 1). The hypoventilation was evident immediately after phrenicotomy and became even more pronounced through the 4 h of the experiment (figs 1 and 2). The decrease of minute ventilation was due to smaller tidal volume and slower rate of breathing (table 1).

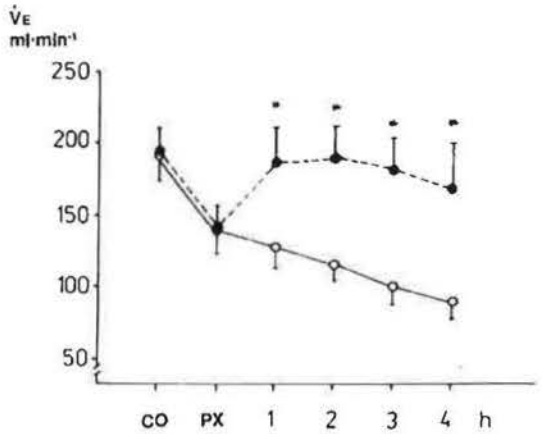

Fig. 1. – Ventilation after phrenicotomy. $\dot{V}_E$: minute ventilation; CO: control measurement before phrenicotomy; PX: measurement immediately after phrenicotomy; 1–4 h: measurements 1–4 h after phrenicotomy; open circles: control group of rats without medication; filled circles: group of rats who received 20 mg·kg^{-1} i.v. aminophylline after phrenicotomy. Bars indicate SD. *p:<0.001 for the difference between groups.

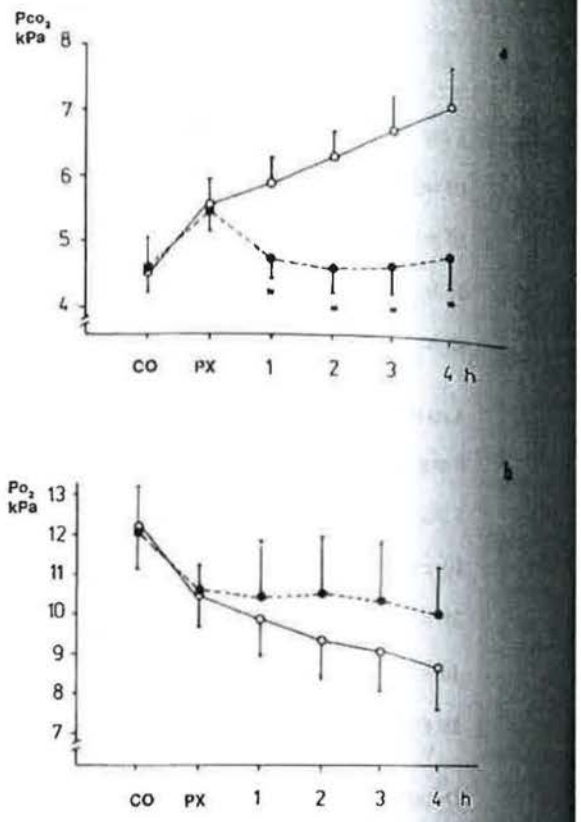

Fig. 2. – Blood gases after phrenicotomy. a: Arterial carbon dioxide partial pressure (Pco_2) and b: arterial oxygen partial pressure (Po_2). The symbols are as in Fig. 1.

The injection of 20 mg·kg^{-1} of AP after phrenicotomy resulted in an increase of ventilation and a decrease of $Paco_2$, which lasted to the end of the experiment (figs 1 and 2). Lower doses of AP (5 and 10 mg·kg^{-1}) had smaller effects which, in the case of 5 mg·kg^{-1}, were not significantly different from controls; after higher doses (40 and 80 mg·kg^{-1}) the effects were more pronounced. This dose-effect relationship was evident 1 h after AP injection (fig. 3). The later time course was different: both the doses smaller and higher than 20 mg·kg^{-1} decreased their effects during the 4 h (fig. 4). These differences after 4 h are statistically significant for 20 and 40 mg·kg^{-1} compared to controls and to 5, 10 and 80 mg·kg^{-1} AP.

The dose of 20 mg·kg^{-1} AP given to the control group 4 h after phrenicotomy resulted in a similar increase of ventilation as in the group of rats who received AP in the same dose immediately after phrenicotomy (table 2). The relative increase of ventilation and the decrease of $Paco_2$ were not statistically different from the corresponding group which received AP (20 mg·kg^{-1}) immediately after phrenicotomy.

The tracheal occlusion pressure increased in controls immediately and at 1 and 2 h after phrenicotomy. A similar increase of tracheal occlusion pressure was observed after all doses of AP. A significantly higher increase was observed with 40 mg·kg^{-1} AP 2 h, and with 80 mg·kg^{-1} 1 h after phrenicotomy.

Table 2. – The effect of 20 mg·kg^{-1} i.v. aminophylline (AP) given 4 h after phrenicotomy.

	f min^{-1}	V_T ml	$\dot{V}_E$ ml·min^{-1}	Ptr kPa	t_I s	t_E s	$Paco_2$ kPa	Pao_2 kPa
CO	108	1.79	193	1.6	0.22	0.35	4.58	12.1
	(13)	(0.17)	(21)	(0.4)	(0.02)	(0.06)	(0.45)	(1.05)
PX	88	1.60	141	1.8	0.25	0.44	5.50	10.4
	(9)	(0.14)	(18)	(0.6)	(0.02)	(0.07)	(0.41)	(0.81)
4 h	69	1.31	90	1.8	0.28	0.61	7.19	8.65
	(7)	(0.15)	(12)	(0.5)	(0.03)	(0.07)	(0.61)	(1.07)
AP 20 mg·kg^{-1}	72*	1.59*	115*	2.3*	0.23*	0.61	6.33*	9.05
	(7)	(0.21)	(20)	(0.6)	(0.02)	(0.12)	(0.81)	(0.82)

Means and standard deviations (in parentheses) are given. f: breathing frequency; V_T: tidal volume; $\dot{V}_E$: minute ventilation; Ptr: tracheal occlusion pressure; t_I: duration of inspiration; t_E: duration of expiration; $Paco_2$: arterial partial pressure of carbon dioxide; Pao_2: arterial partial pressure of oxygen; CO): control measurements before phrenicotomy; PX: measurements immediately after phrenicotomy; 4 h: measurement 4 h after phrenicotomy; AP 20 mg·kg^{-1}: measurements 1 h after AP administration (5 h after phrenicotomy). *$p<0.02$ of the difference between means compared to values 4 h after phrenicotmy.

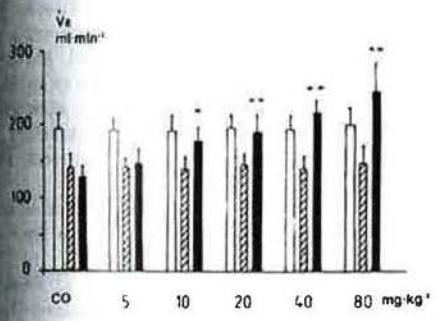

Fig. 3. – Ventilation 1 h after phrenicotomy with different doses of aminophylline. $\dot{V}_E$: minute ventilation; CO: control group without aminophylline; 5–80 mg·kg^{-1}: the respective dose of aminophylline; open bars: control measurements; cross-hatched bars: measurements immediately after phrenicotomy; filled bars: measurements 1 h after administration of aminophylline. Bars indicate one SD. *:$p<0.01$;**: $p<0.001$ for the difference between the means immediately and 1 h after phrenicotomy.

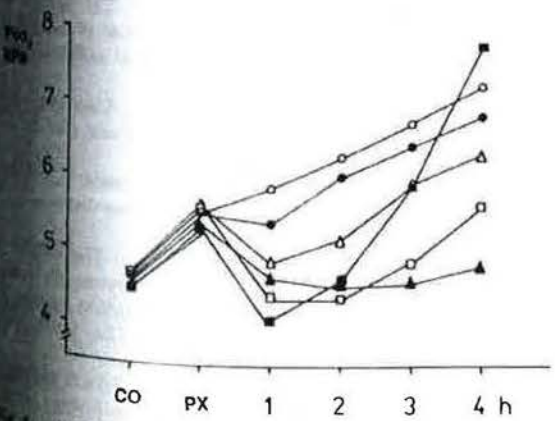

Fig. 4. – Arterial partial pressure of carbon dioxide in rats given 5–80 mg·kg^{-1} i.v. aminophylline (AP) after phrenicotomy. Pco_2: arterial carbon dioxide partial pressure. Symbols on the abscissa are as in Fig. 1. ○—○: control; ●—●: AP 5 mg·kg^{-1}; ∧—∧: AP 10 mg·kg^{-1}; ▲—▲: AP 20 mg·kg^{-1}; □—□: AP 40 mg·kg^{-1}; ■—■: AP 80 mg·kg^{-1}.

Discussion

Respiratory muscle fatigue may occur whenever the energy balance is shifted so that the energy demand exceeds its supply [8, 10]. In phrenicotomized rats the demands on the remaining inspiratory muscles are increased. Their lower efficiency in maintaining adequate ventilation is demonstrated by decreased tidal volume, slower rate of breathing and arterial hypercapnia and hypoxia. By definition, this condition corresponds to respiratory muscle fatigue ("a failure to generate the required or expected force during sustained or repeated contractions" [11]). The possible role of general anaesthesia has been discussed [12; J. Nacházel and F. Palecek unpublished results].

When conditions prediposing to fatigue of respiratory muscles are present, central inhibitory mechanisms prevent their complete exhaustion [13]. Thus, improvement of respiratory muscles function in conditions when they are being fatigued may occur either by central disinhibition, or by improvement of their efficiency.

The central effects of AP are well known and described elsewhere [2]. Therefore, in our experiments we must assume their presence. However, in respiratory muscle fatigue its peripheral effects have also been indicated, both *in vitro* [14–17] and *in vivo* [4–6, 18, 19]. The question arises about the possible proportion of the central stimulating (disinhibitory) and peripheral effects of AP in our phrenicotomized rats. From our results we can gather only a few indirect indices of the peripheral effects of AP on inspiratory muscles. Among them are the insignificantly increased tracheal occlusion pressure after 20 mg·kg^{-1} AP, which has pronounced effects on tidal volume and $Paco_2$, and the fact that increased muscle contractions occurred in spite of shortened recovery period, *i.e.* the duration of expiration.

The peripheral effect of AP is assumed somehow to improve muscle metabolism [20]. This metabolic improvement does not exclude relatively remote effects of AP, such as improved cardiac function or improved muscle perfusion [21]. Also the normocapnic conditions

after AP (as compared with hypercapnia in control rats) may provide a better metabolic environment [22].

We have not measured the plasma levels of AP and therefore cannot compare the various doses directly. We may only take into account that the half-time of AP is approximately 4 h [23, 24]. Thus at the end of our experiments the AP levels after the higher doses might be similar to those of the lower doses immediately after administration. This might also explain the deleterious effect of the highest (80 mg·kg^{-1}) dose of AP after 4 h, which might be due to its prevailing central effects, removal of central inhibition and thus exhaustion of the inspiratory muscles. The possible concomitant beneficial effects on muscle efficiency and thus on their contractility seem to be better balanced with the lower doses, *e.g.* 20 mg·kg^{-1}.

The improvement of the CO_2 level is in sharp contrast with the lack of effect on the postphrenicotomy hypoxaemia (fig. 2). We may assume that in rats after phrenicotomy an inequality of ventilation-perfusion ratios occurs in the dependent parts of the lung, similar to that observed in a patient with diaphragm paralysis [25]. We may presume the existence of poorly ventilated basal parts of the lungs. The increased ventilation after AP would thus compensate for the dead space effects; it cannot, however, improve the hypoxaemia originating in parts with low ventilation-perfusion ratio.

The fact that the effects of AP on breathing of rats 4 h after phrenicotomy were similar to those immediately after the intervention may indicate either: 1) a lack of fatigue of the inspiratory muscles after the 4 h; or 2) no difference in the effect of AP on fresh compared to fatigued muscles, (which is different from the observations of AUBIER *et al.* [6]); or 3) a lack of peripheral effect of AP.

We conclude that AP increases ventilation in a dose-dependent manner in phrenicotomized rats and may thus prevent alveolar hypoventilation.

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L'aminophylline stimule la ventilation chez les rats phrénicotomisés. J. Nacházel, F. Palecek.

RÉSUMÉ: Le but de cette étude est d'établir les effets de l'aminophylline (AP) sur la respiration de rats phrénicotomisé. Cinquante-sept rats mâles Wistar ont été anesthésiés à l'uréthane (1.3 g·kg^{-1} i.p.). Ils ont été phrénicotomisés et divisés en six groupes auxquels étaient donnés respectivement 5, 10, 20, 40 et 80 mg·kg^{-1} AP i.v. ou un volume correspondant de solution saline isotonique. La ventilation, la pression d'occlusion trachéale et les gaz du sang artériel ont été mesurés. Chez tous les animaux, la phrénicotomie a entraîné une hypoventilation avec hypoxémie secondaire (d'une valeur de contrôle de 11.9±1.0 à 10.4±0.8 kPa) et une hypercapnie (d'une valeur contrôle de 4.6±0.5 à 5.5±0.6 kPa). Dans le groupe contrôle (traité à solution saline), après 4 heures, la Pao_2 était de 8.6±1.1 kPa, et la $Paco_2$ de 7.2±0.6 kPa. Après AP, 1 heure après la phrénicotomie, la ventilation minute augmente de manière dose-dépendance de 1–66%; 4 heures après la phrenicotomie, la ventilation minute des rats traités avec 20 et 40 mg·kg^{-1} de AP, était significativement plus élevée que celle du groupe contrôle. L' AP a prévenu l'hypoventilation quand elle a été injectée aux rats phrénicotomisés. Ces résultats fournissent une base non équivoque, qui permet de décider de la fraction centrale et périphèrique des effets de l'aminophylline.

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