

## Changes in phrenic, hypoglossal and recurrent laryngeal nerve activities after intravenous infusions of aminophylline in cats

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*Changes in phrenic, hypoglossal and recurrent laryngeal nerve activities after intravenous infusions of aminophylline in cats. C-H. Chiang, Y-C. Tang, S-E. Wang, J-C. Hwang. ©ERS Journals Ltd 1995.*

**ABSTRACT:** Aminophylline is known to have respiratory stimulant properties, and it has been suggested that it may also be effective in sleep apnoea. However, its role in this disorder remains uncertain. Theoretically, increasing upper airway motoneural activity in order to maintain airway patency might alleviate obstructive sleep apnoea. On the other hand, increasing the respiratory drive may also prove beneficial in treating central sleep apnoea. In these studies, we attempted to determine the effect of aminophylline on neural activities of the upper airway and diaphragm.

We administered intravenously either a low dose (4 mg·kg<sup>-1</sup>) or a high dose (16 mg·kg<sup>-1</sup>) of aminophylline to decerebrated, vagotomized and paralysed cats, and continuously recorded the phrenic hypoglossal and recurrent laryngeal nerve activities for 3 h. Results showed that a high dose of aminophylline induced a marked increase in phrenic nerve activity, but not hypoglossal or recurrent laryngeal nerve activity. In a group treated with a low dosage of aminophylline, a significant increase of activity was found in all three nerves. Furthermore, phrenic nerve activity increased more with a high dose than with a low dose.

We confirmed that aminophylline has dose-dependent and selective effects on respiratory neural activity. A low dose acts on the upper airway and diaphragm, but a high dose induces a marked increase in central respiratory drive. According to our results, low dose aminophylline might be beneficial in obstructive sleep apnoea, whereas, a high or low dose might improve some cases of central sleep apnoea.

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The respiratory stimulant properties of methylxanthine derivatives have been recognized for more than 50 yrs [1]. Aminophylline has been successfully used to treat central apnoea and periodic breathing [2–5], and to decrease Cheyne-Stokes breathing [6, 7]. Furthermore, it has been suggested that this agent may also be effective in treating patients with obstructive sleep apnoea (OSA) [8–10]. However, its effect on neural modulation of respiration in sleep apnoea syndrome remains uncertain.

The mechanism of sleep apnoea syndrome is still unclear. On the basis of clinical studies, the site of obstruction in OSA is typically at the pharyngeal level [11], the main reason suggested for this was that the normal decrease in upper airway muscle activity that occurs at the onset of sleep [12–15] may be sufficient to allow the development of a critical airway collapsing pressure during inspiration [16, 17], when superimposed on a structurally small pharynx [18–20]. Central sleep apnoea is not a single-disease entity, but includes several disorders, in which the definitive event of these disorders is the withdrawal of effective central drive to the respiratory muscles in the rapid eye movement (REM) stage of sleep [21, 22]. Theoretically, inducing an increase in

upper airway motor neural activities (such as hypoglossal and recurrent laryngeal nerves) might be beneficial in the treatment of OSA. However, increasing the respiratory drive would alleviate some cases of central sleep apnoea syndrome.

In the past, the effects of aminophylline on motor nerves of the upper airway and diaphragm have not been explored in detail. In the present study, we intravenously administered either a high or low dose of aminophylline to cats, and continuously recorded the phrenic, hypoglossal and recurrent laryngeal nerve activities. We aimed to evaluate the effect of aminophylline on respiratory neural activities of the upper airway and diaphragm.

### Methods

Fourteen adult cats of either sex were used. The surgical preparation of the animals has been described in detail previously [23, 24]. Under halothane anaesthesia, the trachea was intubated and catheters were placed in femoral arteries and veins. The phrenic, hypoglossal, and recurrent laryngeal nerves were isolated, transected, and prepared for the recording of activities. Bilateral

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vagotomy at the midcervical level and decerebration at the intercollicular level were also carried out. Following decerebration, halothane was discontinued and the animals were paralysed with gallamine and artificially ventilated. End-tidal fractional concentration of  $\text{CO}_2$  ( $F_{\text{ET},\text{CO}_2}$ ) and  $\text{O}_2$  ( $F_{\text{ET},\text{O}_2}$ ) and arterial blood pressure were monitored. The latter was at least 80 mmHg (mean pressure), or was increased to this level by intravenous infusion of metaraminol and/or dextran.  $F_{\text{ET},\text{CO}_2}$  was maintained at 0.06. This level of hypercapnia allowed for more obvious respiratory-related discharges of the hypoglossal nerve [23]. The animals were relatively hyperoxic, with an  $F_{\text{ET},\text{O}_2} > 0.60$ .

Activities of the phrenic, hypoglossal, and recurrent laryngeal nerves were recorded by bipolar electrode. These activities were amplified, electronically filtered (0.6–6.0 kHz), integrated by resistance/capacitance (RC) circuits, and recorded on magnetic tape. Once all the nerve activities were stable, aminophylline was intravenously infused,  $4 \text{ mg}\cdot\text{kg}^{-1}$ , into seven cats, and  $16 \text{ mg}\cdot\text{kg}^{-1}$  into another seven cats. It would have been better to administer both doses to some cats, but due to the long half-life of aminophylline it was impossible in this animal model to wait for the disappearance of the aminophylline effect, in order to observe the effect of a different dosage in the same cat. Each dose was diluted in 3 ml isotonic saline and administered *i.v.* during a 3 min period. Nerve activities before and for 3 h after aminophylline infusion were continuously recorded and played back into our laboratory computer. The following variables were determined: peak integrated nerve activity of phrenic (PNA), hypoglossal (HYNA), recurrent laryngeal nerves during inspiration (RLNA<sub>i</sub>) and expiration (RLNA<sub>e</sub>); inspiratory time (Ti); the total duration of the respiratory cycle (T<sub>tot</sub>); respiratory frequency ( $f_R$ ) and systolic blood pressure (BP<sub>sys</sub>). All variables were expressed as mean  $\pm$  SEM and evaluated statistically by one way

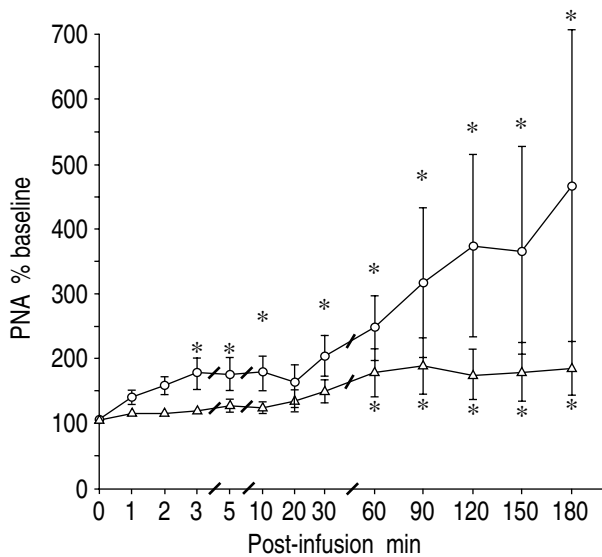


Fig. 1. — Changes in peak integrated phrenic nerve activity (PNA) after aminophylline infusion. Data are presented as mean  $\pm$  SEM. —○—:  $16 \text{ mg}\cdot\text{kg}^{-1}$  (n=7); —△—:  $4 \text{ mg}\cdot\text{kg}^{-1}$  (n=7). Note that the division of the abscissa is not to scale. \*:  $p < 0.05$  compared to baseline.

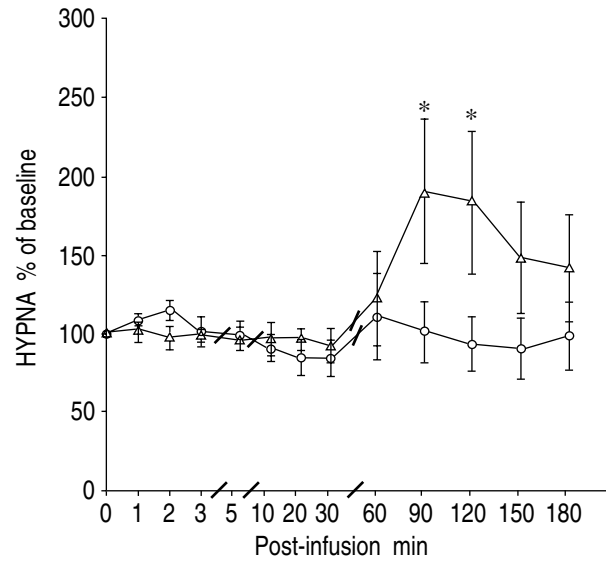


Fig. 2. — Changes in peak integrated hypoglossal nerve activity (HYPNA) after aminophylline infusion. Data are presented as mean  $\pm$  SEM. —○—:  $16 \text{ mg}\cdot\text{kg}^{-1}$  (n=7); —△—:  $4 \text{ mg}\cdot\text{kg}^{-1}$  (n=7). Note that the division of the abscissa is not to scale. \*:  $p < 0.05$  compared to baseline.

analysis of variance (ANOVA) with repeat measurement, followed by F-test to compare before (0 min) and after aminophylline infusion at all time intervals (1, 2, 3, 5, 10, 20, 30, 60, 90, 120, 150 and 180 min) respectively. Statistical analyses were performed using the computer program Statview (Brain Power Inc., Calabasa, CA, USA) and a  $p < 0.05$  was considered statistically significant.

## Results

All peak integrated nerve activities of phrenic, hypoglossal, and recurrent laryngeal nerves are reported in figures 1–4 and the changes of respiratory frequency, systolic

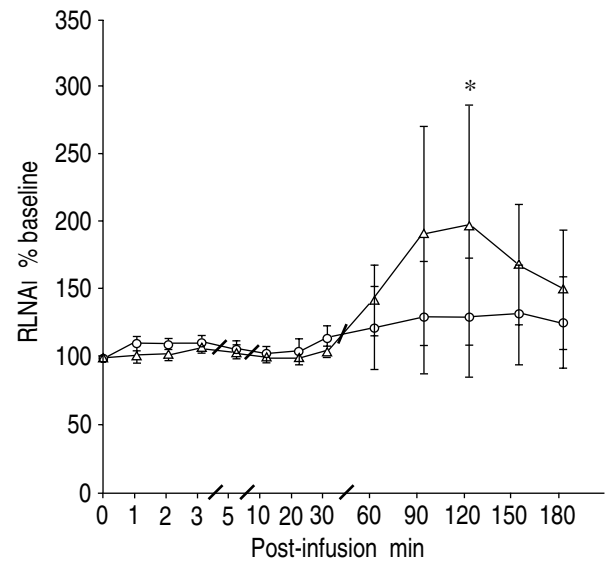


Fig. 3. — Changes in peak integrated recurrent laryngeal nerve activity during inspiration (RLNA<sub>i</sub>) after aminophylline infusion. Data are presented as mean  $\pm$  SEM. —○—:  $16 \text{ mg}\cdot\text{kg}^{-1}$  (n=7); —△—:  $4 \text{ mg}\cdot\text{kg}^{-1}$  (n=7). Note that the division of the abscissa is not to scale. \*:  $p < 0.05$  compared to baseline.

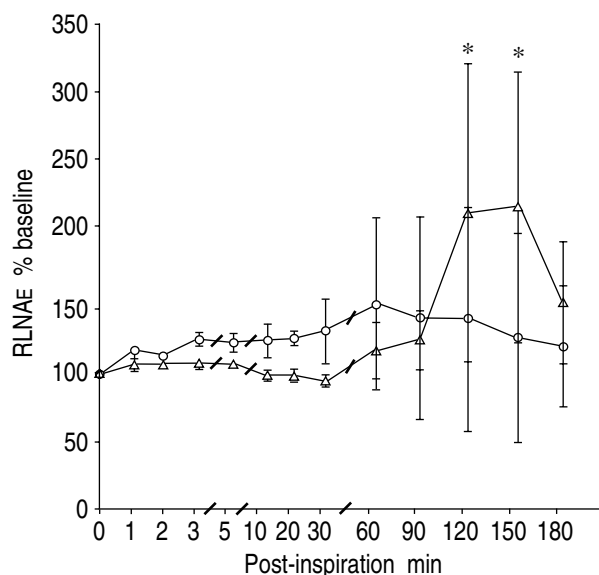


Fig. 4. — Changes in peak integrated recurrent laryngeal nerve activity during expiration (RLNAE) after aminophylline infusion. Data are presented as mean±SEM. —○—: 16 mg·kg<sup>-1</sup> (n=7); —△—: 4 mg·kg<sup>-1</sup> (n=7). Note that the division of the abscissa is not to scale. \*: p<0.05 compared to baseline.

blood pressure and inspiratory time are indicated in table 1. Figures 1–4 present changes in peak integrated nerve activities of phrenic, hypoglossal, and recurrent laryngeal nerves in the inspiratory or expiratory phase over time. With a high dose of *i.v.* aminophylline (16 mg·kg<sup>-1</sup>), peak integrated phrenic nerve activity (PNA) rose continuously during the 3 h observation period. The increase was significant from the third minute (fig. 1). With a low dose of *i.v.* aminophylline (4 mg·kg<sup>-1</sup>), PNA increased from the 60th minute. The increase in PNA was greater with the high rather than the low dose, but due to too large an SEM, statistical significance (p<0.05, comparing the high and low dose with t-test) was found only at 1, 2, 3 and 5 min.

The hypoglossal nerve activity did not change with high doses of aminophylline, but significant increases with low doses were found at 90 and 120 min (fig. 2).

Similarly, recurrent laryngeal nerve activity (RLNA) did not change with high doses of aminophylline, but reached a level of significant increase with low doses of aminophylline at 120 min in the inspiratory phase, and at 120 and 150 min in the expiratory phase (figs. 3 and 4).

No significant changes in arterial blood pressure and respiratory frequency were found with either dose (table 1). A significant decrease in inspiratory time had developed 90 min after the administration of a high dose of aminophylline, but no change in inspiratory time was found with a low dose infusion.

## Discussion

In the past, HWANG *et al.* [23] showed that activity of the hypoglossal nerve is depressed more than other nerves following subanaesthetic doses of halothane, pentobarbital, or ketamine, and therefore it is difficult to detect hypoglossal activity in the anaesthetized animal. In order to record hypoglossal neural activity more easily, decerebrated cats under hypercapnic conditions were used in our model. Where no anaesthetic effects remain, none of the above-mentioned agents had been used.

Our results are similar to those of previous studies, which showed significant increases in ventilatory response [25], as well as phrenic nerve activity administration after aminophylline [26]. Additionally, we found that aminophylline exhibited a dose-dependent phenomenon: greater phrenic nerve activity was evident when a high (16 mg·kg<sup>-1</sup>) vs a low (4 mg·kg<sup>-1</sup>) dosage was given. Meanwhile, PNA increase approached a peak at 90 min with a low aminophylline infusion, but continued to increase gradually and had the highest value 3 h after a high dose aminophylline infusion.

The mechanism of aminophylline and how to modulate phrenic nerve activity remains unclear. Earlier studies showed that respiratory responses induced by aminophylline do not require vagal reflexes, carotid body chemoreceptors [26, 27], release of catecholamine from the adrenal gland [28], suprapontine brain and spinal cord [27]. On the basis of the above-mentioned studies, the

Table 1. — Changes of respiratory frequency, arterial blood pressure and inspiratory time after aminophylline infusion

Time min	<i>f</i> <sub>R</sub> breath·min <sup>-1</sup>		BP <sub>sys</sub> mmHg		T <sub>i</sub> s	
	4 mg	16 mg	4 mg	16 mg	4 mg	16 mg
0	16.6±2.7	14.1±1.2	150±8	100±14	1.04±0.19	1.77±0.10
1	16.4±2.7	13.9±1.1	159±5	123±10	1.07±0.18	1.75±0.23
2	16.1±2.5	14.2±1.3	158±4	129±10	1.04±0.18	1.72±0.29
3	16.5±2.7	14.4±1.3	152±9	140±9	1.03±0.18	1.73±0.44
5	16.7±2.7	14.3±1.2	156±5	141±6	1.04±0.17	1.70±0.41
10	16.5±2.6	14.5±1.2	152±7	134±4	1.10±0.18	1.50±0.29
20	16.3±2.5	16.4±1.5	153±11	131±7	1.08±0.17	1.43±0.24
30	16.2±2.5	16.8±1.4	148±11	117±10	1.08±0.19	1.38±0.15
60	16.3±2.6	16.9±1.7	142±8	105±10	1.11±0.20	1.41±0.18
90	16.3±2.6	16.5±1.5	141±8	114±15	1.15±0.24	1.25±0.14*
120	16.5±2.7	16.6±1.5	131±18	98±18	1.09±0.24	1.15±0.14*
150	16.3±2.6	16.6±1.6	149±15	96±17	1.25±0.19	1.15±0.15*
180	16.3±2.6	16.2±1.4	146±17	88±18	1.16±0.17	1.15±0.17*

All values are expressed as mean±SEM. *f*<sub>R</sub>: respiratory frequency; BP<sub>sys</sub>: systolic blood pressure; T<sub>i</sub>: inspiratory time. \*: p<0.05 compared to baseline.

increase in phrenic nerve activity following the administration of aminophylline, might have resulted from the action of aminophylline on the brain stem [27]. The specific brain stem structures on which aminophylline acts are undefined. It has been proposed that aminophylline alters the sensitivity of the central chemoreceptors and/or afferent fibres from these chemoreceptors [29]. In addition, aminophylline may have a direct action upon respiratory motorneurons or neurons impinging upon them. The cellular mechanism by which aminophylline produces changes in neuronal activity is not well explored, and appears to be multiple. Aminophylline might modulate other neurotransmitters, such as dopamine, serotonin and gamma-aminobutyric acid (GABA) [30, 31]. Meanwhile, past studies have shown that the stimulant effect of aminophylline involves phosphodiesterase inhibition at a high dose, and blockade of adenosine receptors at a low dose [32]. Therefore, the dose of aminophylline administered might influence respiratory response.

Our other major finding, the effect of aminophylline on motor nerves innervating muscles of the upper airway, shows that a low dose of aminophylline ( $4 \text{ mg}\cdot\text{kg}^{-1}$ ) significantly increased recurrent laryngeal and hypoglossal nerve activity at about 90 min. However, recently ST JOHN and BARTLETT [26] found no significant changes in hypoglossal activity after aminophylline administration. The discrepancy in results might be due to the period of observation, where the duration of study may have been too brief (8–32 min) to detect a change.

In our results, a low dosage of aminophylline acted selectively upon upper airway motor nerves, whilst a high dosage acted upon phrenic nerves. Similarly, the selective action was found in other (including human) studies. LAHIVE *et al.* [33] showed that a low dose of aminophylline selectively increased the electromyographic (EMG) activities of the nasal alae of normal subjects, and speculated that a low dose of aminophylline produces a selective increase in upper airway muscle activity. Selective actions were also found with other drugs: BONORA *et al.* [34] studied the neural activity of the hypoglossal and phrenic nerves in cats. Their results demonstrated a selective decrease in hypoglossal neural activity after the administration of diazepam, but a selective increase after the administration of protriptyline. However, the mechanism of this selective action is unclear. Considerable evidence has been found to support the theory of a differing control mechanism between the upper airway and the respiratory muscle [35–37]. Furthermore, the action of aminophylline on different sites has been suggested: neural control of upper airway musculature is altered by activity within the reticular activating system [33, 35], but phrenic activity is controlled in the respiratory centre [26, 27].

Adenosine had been considered as a neuromodulator in central respiratory regulation [38], and may tonically suppress activity in the reticular activating system and respiratory centre, either directly or through its inhibition of the excitatory neurotransmitter. A low dose of aminophylline, causing a blockade of adenosine receptors, would reverse this suppression, leading to increased activity of the reticular activating system and respiratory centre,

which would result in an increase in respiratory neural activity of the upper airway and phrenic nerve. However, a high dose of aminophylline causes different actions, among which are cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) phosphodiesterase inhibition. The effect of phosphodiesterase inhibition on the respiratory centre and reticular activating system is unclear. Furthermore, it is unknown why a high dose of aminophylline, with the action of phosphodiesterase, has an effect on the respiratory centre which results in a marked increase of phrenic nerve activity, but no action on the control of the upper airway. Based on the above information, the mechanism of the dose-dependent and selective effect of aminophylline could be multiple and complex, with the exception of different control systems between the respiratory motor nerves of the upper airway and diaphragm. We speculate that these two control systems might contain a different neuron composition, and, furthermore, that these neurons might have different amounts of receptors of adenosine, phosphodiesterase or other neurotransmitters. This hypothesis, however, needs further investigation.

There were limitations in our animal model when studying neural activity during the sleep stage. However, an alternative animal model could be used to determine which drugs have the potential to increase neural activities of the upper airway and diaphragm and, furthermore, to screen which drugs might be beneficial for sleep apnoea. Therefore, these animal results can be used as a reference for further human studies regarding which drugs are candidates for clinical trial in patients with sleep apnoea.

In summary, our studies show that aminophylline has dose-dependent and selective effects. A low dose acts on the upper airway motor activities, which are reflected by an increase in neural activities of the hypoglossal and recurrent laryngeal nerves which might be beneficial for sleep apnoea, but a high or low dose induces stimulation of respiration, as manifest by an increase in phrenic nerve activity which might be beneficial for some cases of central sleep apnoea. However, whether aminophylline has a therapeutic effect on sleep apnoea still requires further extensive clinical investigation.

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