

Endogenous opiates and the control of breathing in normal subjects and patients with chronic airflow obstruction

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ABSTRACT To investigate the role of endorphins in central respiratory control, the effect of naloxone, a specific opiate antagonist, on resting ventilation and ventilatory control was investigated in a randomised double-blind, placebo-controlled study of normal subjects and patients with chronic airways obstruction and mild hypercapnia due to longstanding chronic bronchitis. In 13 normal subjects the ventilatory response to hypercapnia increased after an intravenous injection of naloxone (0.1 mg/kg), ventilation ($\dot{V}E$) at a PCO_2 of 8.5 kPa increasing from $55.6 \pm \text{SEM } 6.2$ to $75.9 \pm 8.2 \text{ l min}^{-1}$ ($p < 0.001$) and the $\Delta\dot{V}E/\Delta\text{PCO}_2$ slope increasing from 28.6 ± 4.4 to $34.2 \pm 4.2 \text{ l min}^{-1} \text{ kPa}^{-1}$ ($p < 0.05$). There was no significant change after placebo (saline) injection. Naloxone had no effect on resting ventilation or on the ventilatory response to hypoxia in normal subjects. In all six patients naloxone significantly ($p < 0.02$) increased mouth occlusion pressure ($P_{0.1}$) responses to hypercapnia. Although there was no change in resting respiratory frequency or tidal volume patients showed a significant ($p < 0.01$) decrease in inspiratory timing (T_i/T_{tot}) and increase in mean inspiratory flow (V_T/T_i) after naloxone. These results indicate that endorphins have a modulatory role in the central respiratory response to hypercapnia in both normal subjects and patients with airways obstruction. In addition, they have an inhibitory effect on the control of tidal breathing in patients with chronic bronchitis.

Exogenous opiates have long been known to depress respiration and diminish the ventilatory response to hypoxia and hypercapnia.¹ These effects are blocked by naloxone, a potent and specific opiate receptor antagonist.² Endogenous opiates (endorphins)^{3,4} and opiate receptors have been found in high concentration in the solitary nuclei and area postrema of the medulla,⁵ areas closely associated with central control of respiration. This has suggested that endorphins may play a part in the central control of breathing.

Animal studies have indicated that endorphins may be important in central respiratory control. Injection of methionine-enkephalin into the brain stem induced a fall in resting ventilation and tidal volume in cats.⁶ Intracisternal injection of human β -endorphin produced a similar effect in dogs and also caused diminution of respiratory sensitivity to

carbon dioxide.⁷ Naloxone led to increased phrenic nerve output in cats,⁸ shortened apnoeic episodes in newborn asphyxiated rabbits,⁹ and an increased respiratory response to carbon dioxide in dogs,¹⁰ suggesting that endorphins may influence central control of respiration.

In normal man naloxone had no effect on tidal volume or on end-tidal carbon dioxide.¹¹ In a small study naloxone had no significant effect on ventilatory responses to hypercapnia or hypoxia in normal subjects.¹² In patients with chronic airway obstruction, however, naloxone increased the ability to compensate for an additional inspiratory resistance and in some patients increased the response to carbon dioxide.¹³ This study, however, lacked placebo controls, making interpretation difficult. As the role of endogenous opiates in the control of breathing remains uncertain, we have studied the effects of naloxone on respiration and ventilatory control in normal subjects and in patients with chronic airway obstruction in a double-blind randomised study.

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Table 1 Forced expiratory volume in one second (FEV_1), vital capacity (VC), and mixed venous carbon dioxide tension ($PvCO_2$) in patients with chronic airways obstruction as a result of longstanding chronic bronchitis

Patient No	Age (y)	FEV_1 (l)	VC (l)	$PvCO_2$ (kPa)
1	56	0.41	2.49	7.1
2	57	0.56	2.57	6.9
3	62	0.90	1.96	7.0
4	63	0.46	1.95	7.7
5	69	0.53	2.24	7.2
6	71	0.67	2.76	7.3
Mean	63.0	0.59	2.33	7.2

Methods

We studied 13 normal subjects (10 of them men) aged 23–43 years, none of whom took medication or smoked; and six patients with severe chronic obstructive airways disease with a forced expiratory volume in one second (FEV_1) of less than 1 litre (table 1). All had mild hypercapnia (mixed venous carbon dioxide tension ($PvCO_2$) 6.9–7.7 kPa). All medication was stopped 12 hours before the study and tea and coffee were avoided by all subjects for the previous six hours. The research ethics committee approved the investigation and all subjects gave informed consent.

To avoid the effect of a mouthpiece, resting ventilation was measured non-invasively from body surface movements with a respiratory inductance plethysmograph (Respirtrace) consisting of thoracic and abdominal belts. This was calibrated by an isovolume manoeuvre as previously described¹⁴ and gave an accuracy compared with simultaneous spirometric measurements in the semi-recumbent posture of $\pm 10\%$ in both normal subjects and patients with airways obstruction. Measurements were made with the subject lying quietly and when ventilation showed little variation a sample over five minutes was recorded (Sanborn recorder) with a paper speed of 1 cm/s. Resting respiratory frequency, tidal volume (VT), inspiratory timing (Ti/Ttot), and mean inspiratory flow (VT/Ti) were measured.¹⁵

Respiratory sensitivity to carbon dioxide was measured by a modification of the rebreathing method of Read.¹⁶ Subjects rebreathed a 5% carbon dioxide in 95% oxygen gas mixture from an anaesthetic bag contained in a glass bottle and ventilation was measured by a dry gas meter (Parkinson Cowan CD4). Gas was continuously sampled at the mouth by an infrared carbon dioxide meter (Capnograph, Godart) and the sampled gas was returned to the rebreathing bag. In the patients mouth pressure in the first 0.1 second of an occluded breath ($P_{0.1}$) was measured with a specially designed

valve, and measurements were made every 30 seconds during rebreathing. $P_{0.1}$ is independent of the compliance and flow resistance of the lung,^{17 18} and therefore provides a better index of central respiratory drive than does ventilation in patients with airway obstruction, whose ventilatory response may be limited. Results were analysed by plotting ventilation ($\dot{V}E$) and $P_{0.1}$ against PCO_2 . The resulting plots were linear and the slopes determined by linear regression analysis ($\Delta \dot{V}E/\Delta PCO_2$; $\Delta P_{0.1}/\Delta PCO_2$). $\dot{V}E$ or $P_{0.1}$ at a fixed PCO_2 (8.5 kPa) was also determined.

Hypoxic responses were measured in normal subjects by a modification of the method of Rebuck and Campbell.¹⁹ Subjects rebreathed a gas mixture of 7% carbon dioxide in air and ventilation was measured as above. Before rebreathing subjects breathed quietly on the mouthpiece connected to air and end-tidal PCO_2 was estimated. This was then maintained at the same level ($\pm 0.2\%$) throughout the rebreathing period by a scrub circuit (containing soda lime) with a variable flow. Arterial oxygen saturation (SaO_2) was measured continuously by an ear oximeter (Hewlett Packard). Rebreathing continued until the SaO_2 fell to 70%. The resulting plots of $\dot{V}E$ against SaO_2 were linear and the slopes ($\Delta \dot{V}E/\Delta SaO_2$) were determined by linear regression analysis.

Baseline measurements of resting ventilation and hypercapnia response were made in all subjects, and hypoxic response in eight normal subjects. Subjects were then given either naloxone 0.1 mg/kg or volume-matched saline in double-blind manner on consecutive days. This large dose of naloxone was chosen to block endogenous opiate receptors completely. Measurements were repeated 10 minutes after injection, which is sufficient time to allow penetration of naloxone into the brain; and studies were completed within 40 minutes of injection, which is well within the half life of the drug.²⁰ No subjects knew whether they had received naloxone or placebo and no adverse effects were reported. Heart rate and blood pressure were recorded periodically.

Results were analysed statistically by the paired Student's t test.

Results

NORMAL SUBJECTS

There was no significant change in resting minute ventilation ($\dot{V}E$), respiratory frequency, tidal volume (VT), Ti/Ttot or VT/Ti with either naloxone or placebo (table 2). There was no significant change in hypnotic response ($\Delta \dot{V}E/\Delta SaO_2$) after either placebo or naloxone in eight subjects, although the hypoxic response showed considerable variability, as reported by others.²¹ In 13 subjects the mean response to

Table 2 Mean (\pm SEM) respiratory responses to naloxone and placebo in normal subjects

	Placebo		Naloxone	
	Before	After	Before	After
<i>Resting ventilation (n = 8)</i>				
$\dot{V}E$ ($l \text{ min}^{-1}$)	5.81 \pm 0.30	5.99 \pm 0.26	6.21 \pm 0.28	5.75 \pm 0.25
Respiratory frequency (breaths/min)	14.5 \pm 0.7	13.9 \pm 0.9	15.7 \pm 1.1	14.3 \pm 1.0
Tidal volume (l)	0.40 \pm 0.07	0.43 \pm 0.05	0.40 \pm 0.07	0.40 \pm 0.07
V_T/T_i ($l \text{ s}^{-1}$) (n = 5)	0.26 \pm 0.02	0.35 \pm 0.05	0.29 \pm 0.09	0.32 \pm 0.03
Ti/Ttot (n = 5)	0.38 \pm 0.01	0.33 \pm 0.03	0.36 \pm 0.03	0.33 \pm 0.02
<i>Hypercapnic response (n = 13)</i>				
$\Delta\dot{V}E/\Delta PCO_2$ ($l \text{ min}^{-1} \text{ kPa}^{-1}$)	25.9 \pm 3.4	26.7 \pm 3.3	28.6 \pm 4.4	34.2 \pm 4.2*
$\dot{V}E$ at $PCO_2 = 8.5 \text{ kPa}$ ($l \text{ min}^{-1}$)	56.7 \pm 6.9	58.4 \pm 6.6	56.6 \pm 6.2	75.9 \pm 8.3***
<i>Hypoxic response (n = 8)</i>				
$\Delta\dot{V}E/\Delta SaO_2$ (l/min/%sat)	1.44 \pm 0.26	1.68 \pm 0.34	1.35 \pm 0.40	1.49 \pm 0.31

Significance of difference between values before and after injection: *** p < 0.001; * p < 0.05.

carbon dioxide was significantly increased after naloxone whether measured by slope ($\Delta\dot{V}E/\Delta PCO_2$) or by ventilation at a fixed carbon dioxide tension ($\dot{V}E$ at $PCO_2 = 8.5 \text{ kPa}$) but there was no significant change after placebo (fig 1). There was no significant difference between the preinjection hypercapnic responses on the different study days. There was considerable individual variability in response to naloxone, some subjects showing a considerable response whereas others showed little change. There was no significant correlation, however, between magnitude of response to naloxone and the initial sensitivity to carbon dioxide. Reproducibility was assessed in one subject who showed a large response to naloxone, which was observed under double-blind conditions on three separate occasions.

PATIENTS

There were no significant changes in either resting $\dot{V}E$, respiratory frequency, or V_T in the patients, although there was a significant fall in Ti/T_{tot} ($p < 0.01$) and a significant rise in V_T/T_i ($p < 0.01$) after naloxone, but not after placebo (table 3, fig 2). As expected, the ventilatory responses to carbon dioxide were much lower than in normal subjects. The slope of the ventilatory response to hypercapnia ($\Delta\dot{V}E/\Delta PCO_2$) and the ventilation at $PCO_2 = 8.5 \text{ kPa}$ increased with naloxone but this trend did not achieve significance. The slope of the $P_{O_{2}}$ response ($\Delta P_{O_{2}}/\Delta PCO_2$) was, however, significantly greater ($p < 0.02$) after naloxone than after placebo, and the $P_{O_{2}}$ at $PCO_2 = 8.5 \text{ kPa}$ was significantly higher ($p < 0.02$) after naloxone than after placebo (fig 3).

There were no significant changes in heart rate or blood pressure with naloxone in either normal subjects or patients.

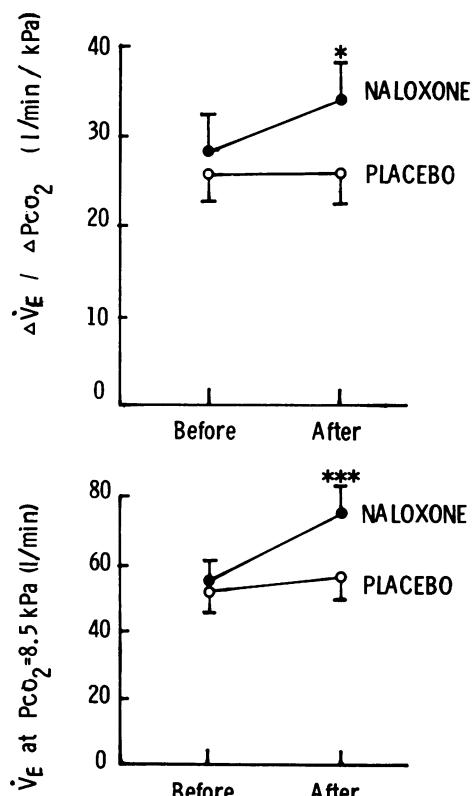


Fig 1 Slope of ventilatory response (means \pm SEM) to hypercapnia ($\Delta\dot{V}E/\Delta PCO_2$) (above) and ventilation at a PCO_2 of 8.5 kPa (below) in 13 normal subjects before and after injection of naloxone or placebo. Significance of difference between values before and after injection: *** p < 0.001; * p < 0.05.

Table 3 Mean (\pm SEM) respiratory responses to naloxone and placebo in six patients with chronic bronchitis

	Placebo		Naloxone	
	Before	After	Before	After
<i>Resting ventilation</i>				
VE ($l \text{ min}^{-1}$)	8.32 \pm 0.75	8.04 \pm 0.77	8.06 \pm 0.77	9.43 \pm 1.44
Respiratory frequency (breaths/min)	17.9 \pm 2.7	17.2 \pm 2.1	18.5 \pm 2.4	18.5 \pm 2.5
Tidal volume (l)	0.50 \pm 0.06	0.49 \pm 0.05	0.47 \pm 0.05	0.52 \pm 0.05
VT/Ti ($l \text{ s}^{-1}$)	0.47 \pm 0.06	0.47 \pm 0.07	0.45 \pm 0.07	0.66 \pm 0.12***
Ti/Ttot	0.31 \pm 0.03	0.31 \pm 0.03	0.32 \pm 0.03	0.26 \pm 0.02***
<i>Hypercapnic response</i>				
$\Delta VE/\Delta PCO_2$ ($l \text{ min}^{-1} \text{kPa}^{-1}$)	3.63 \pm 0.60	3.44 \pm 0.49	3.10 \pm 0.51	3.87 \pm 1.05
VE at $PCO_2 = 8.5 \text{ kPa}$ ($l \text{ min}^{-1}$)	15.1 \pm 0.7	14.5 \pm 0.8	14.2 \pm 0.6	15.7 \pm 1.0
$\Delta P_{o_1}/\Delta PCO_2$	0.042 \pm 0.008	0.040 \pm 0.009	0.038 \pm 0.009	0.065 \pm 0.013**
P_{o_1} at $PCO_2 = 8.5 \text{ kPa}$ (kPa)	1.13 \pm 0.17	1.10 \pm 0.17	1.08 \pm 0.15	1.36 \pm 0.21**

Significance of difference between values before and after injection: *** $p < 0.01$; ** $p < 0.02$.

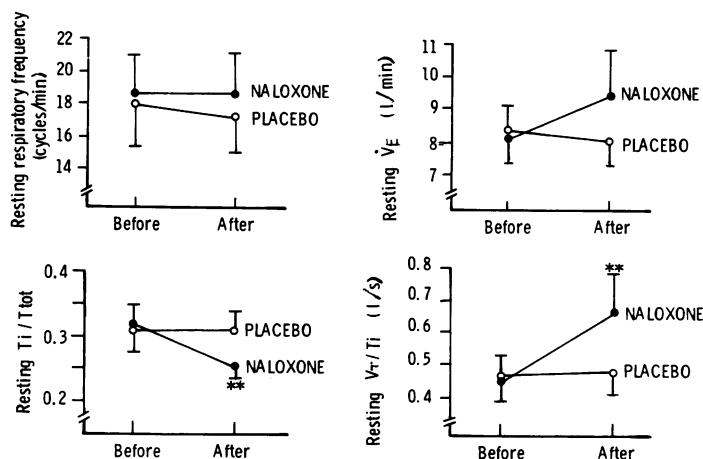


Fig 2 Resting ventilation in six patients with chronic obstructive airway disease before and after injection of naloxone or placebo: mean (\pm SEM) respiratory frequency, minute ventilation (VE), inspiratory timing (Ti/Ttot), and mean inspiratory flow (VT/Ti). Significance of difference between values before and after injection: ** $p < 0.01$.

Discussion

Our results indicate that endorphins have played a modulatory role in the control of breathing. In both normal subjects and patients with chronic airflow obstruction and mild hypercapnia the ventilatory response to carbon dioxide was significantly increased by naloxone given in a randomised double-blind manner. In normal subjects both the slope of the hypercapnic response and the ventilation at a given carbon dioxide tension were increased. In patients the hypercapnic response measured by slope and position was similarly increased when P_{o_1} was used to measure response. Although the ventilatory response to hypercapnia showed a tendency to increase with naloxone in the patients this trend did not achieve statistical significance because of the greater variability of ventilatory response and the mechanical limitations of severe airflow obstruction

that greatly reduced the ventilatory response. These results suggest that endorphins have an inhibitory effect in the central respiratory response to hypercapnia. In normal subjects there was individual variability in the magnitude of the effect of naloxone on the hypercapnic response, and some subjects were not affected by naloxone. There was no correlation, however, between the magnitude of response and the initial ventilatory response to hypercapnia, indicating that differing influences of endorphins are unlikely to account for individual variations in the ventilatory response to carbon dioxide.²² All six patients with chronic bronchitis, however, showed an increase in the P_{o_1} response to carbon dioxide with naloxone. Our results are at variance with those of Fleetham *et al.*,¹² who found no significant effect of naloxone on hypercapnic responses in six normal subjects. Although they found an increase in the slope of the relationship between ventilation and carbon dioxide

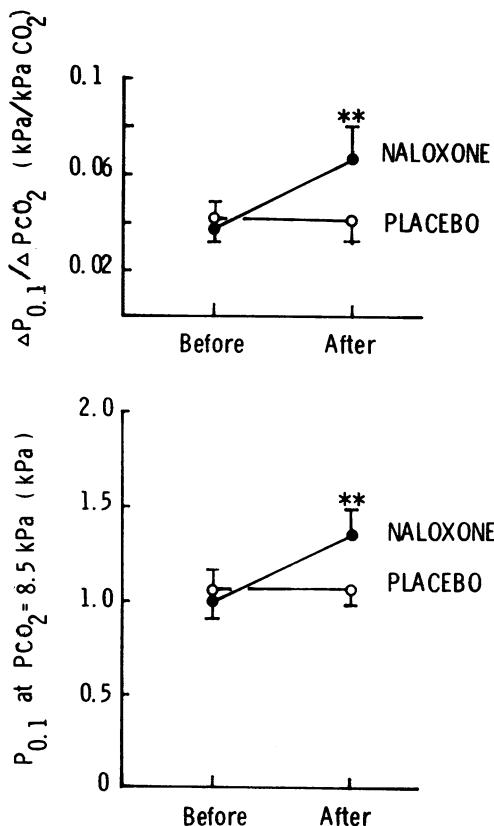


Fig 3 Slope of mouth occlusion pressure response to hypercapnia ($\Delta P_{0.1}/\Delta PCO_2$) (above) and $P_{0.1}$ response at a PCO_2 of 8.5 kPa (below) (means \pm SEM) in six patients with chronic obstructive airway disease before and after injection of naloxone or placebo. Significance of difference between values before and after injection: ** $p < 0.02$.

tension with naloxone they observed a similar change with placebo, whereas in our study no placebo response was observed. Santiago *et al*¹³ found that naloxone increased the $P_{0.1}$ response to hypercapnia in some patients with mild airways obstruction and increased the respiratory effort elicited by an added inspiratory airway resistance in others. These responses were not compared with placebo, however, and must therefore be interpreted with some caution.

In normal subjects naloxone had no significant effect on resting ventilation or pattern of breathing. In the patients, although naloxone did not affect tidal volume or respiratory frequency, there was a significant increase in resting mean inspiratory flow (V_T/T_i) and decrease in inspiratory timing (T_i/T_{tot}), which may indicate an increased neuronal output

from the respiratory centre. This suggests that endorphins may have a modulatory influence on tidal breathing in patients with chronic airways obstruction.

Hypoxic drive is mediated mainly through peripheral chemoceptors in the carotid body.²³ Recent histochemical studies have shown a high concentration of endogenous opiates in the carotid body of cats,^{24 25} suggesting that endorphins may have a modulatory role in hypoxic drive. There is experimental evidence that naloxone does increase hypoxic responses in the cat.²⁶ In our study no significant change in hypoxic responses after naloxone was found, although the variability of this response may have masked a small effect.

The effects of naloxone are small, however. More than one type of opiate receptor has been defined,^{27 28} and whereas naloxone is a potent antagonist against mu receptors it is much less potent against delta and kappa receptors, which could also play a part in the central control of respiration.

Because the effects of naloxone are small the clinical application of these findings is probably limited. Although naloxone lacks appreciable side effects, even in large doses, it is obviously less potent than other analeptics, although occasional patients may show large responses. Our studies do show that endorphins have a modulatory role in the respiratory response to carbon dioxide in both normal subjects and patients with chronic airflow obstruction, and also have an inhibitory effect on tidal breathing in these patients. Changes in medullary endorphin concentrations may therefore influence the control of breathing.

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