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Peripheral cardiorespiratory effects of bombesin in anaesthetized rats

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ABSTRACT

The respiratory effects evoked by systemic injection of bombesin were studied in spontaneously breathing rats that were (i) neurally intact and subsequently bilaterally vagotomized, (ii) intact, before and after pharmacological blockade of the bombesin BB_1 and BB_2 receptors. An intravenous bolus of bombesin (10 μg/kg) evoked sighs, decrease in the breathing rate, augmentation of tidal volume and an increase in mean arterial blood pressure. Midcervical vagotomy abolished all respiratory changes evoked by bombesin challenge, but did not prevent the increase in blood pressure. Blockade of BB_1 and BB_2 receptors with an intravenous dose of 50 μg/kg of $[D\text{-Phe}]^{12}$-bombesin, reduced significantly the cardio-respiratory effects due to bombesin administration. The BB_1 receptors antagonist, BIM 23127, at a dose of 100 μg/kg did not block the response to bombesin. These results indicate that bombesin given systemically stimulates ventilation by activation of BB_2 receptors affecting mainly the tidal component of the breathing pattern, and that the response is mediated by the lung vagi. The hypertensive effect of bombesin resulted from the excitation of BB_2 receptors, but occurred outside vagal afferentation from the lungs.

1. Introduction

Bombesin and gastrin releasing peptide (GRP) together belong to the bombesin-like peptide family. They are structurally and functionally homologous, binding to the same high-affinity bombesin/GRP-preferring receptor-BB_2 (Ashour et al., 2006).

Bombesin, a neuropeptide isolated from the skin of the frog *Bombina bombina*, is biologically active in mammals, acting as a neuroregulator of physiological functions including memory, body temperature, blood pressure and gastrointestinal tract functions (Ohki-Hamazaki et al., 2005; Yeğen, 2003).

Several published findings demonstrated that bombesin-like peptides and receptors are involved in normal lung development (Emanuel et al., 1999; Shan et al., 2004), contribute to lung injury of premature infants with bronchopulmonary dysplasia (Ashour et al., 2006) and to human lung carcinogenesis (Yeğen, 2003). Mitogenic and anti-inflammatory properties of bombesin have also been described (Yeğen, 2003; Jensen et al., 2008).

Furthermore, bombesin is considered to be involved in the regulation of respiration in mammals. Indeed, within the central nervous system high bombesin-like immunoreactivities were detected, including in the nucleus tractus solitarii (Jensen et al., 2008; Moody and Merali, 2004). In one of the early studies, it was demonstrated that bombesin given intracerebroventricularly (i.c.v.) or injected into the area of the nucleus ambiguus of the rat caused a prolonged increase in tidal volume and slowing down of breathing. Yet, microinjections of this peptide into the nucleus tractus solitarii increased tidal volume and respiratory rate, with sporadic episodes of apnoea (Hedner et al., 1985). Another more recent finding showed only an augmentation of tidal volume in response to bombesin microinjected to nucleus tractus solitarii (Glazkova and Inyushkin, 2006).

Of particular interest is that the respiratory action of centrally applied bombesin has been studied in detail, whereas there are very few experimental data on the systemic challenge. At the periphery, bombesin-like BB_1, BB_2, BB_3 receptors are localized in the lungs, within mucosal neuroendocrine, non-neuroendocrine epithelial cells, and mesenchymal cells in humans, rodents and nonhuman primates (Emanuel et al., 1999; Shan et al., 2004; Ghatei et al., 1983; Kane et al., 1996). The contribution of peripheral bombesin receptors to respiratory reflexes is far from clear. Two reports on the actions of systemic bombesin showed the enhancement of the pulmonary chemoreflex provoked by capsaicin in rats, mediated by pulmonary C-fibers (Gu and Lee, 2005) and the contraction of bronchial smooth muscle of the guinea-pig in vitro (Lach et al., 1993).

Presumably excitation of receptors situated in the intrapulmonary airway, accessible via the pulmonary circulation, might have a modulatory effect on the respiratory pattern. However, we have not found any report quantifying merely the cardiorespiratory response to systemic administration of bombesin. Such knowledge could be of importance since release of bombesin is enhanced in pathological conditions e.g. by lung neuroendocrine cells after tobacco exposure, in chronic obstructive pulmonary disease and eosinophilic granuloma (Bergren, 2002; Aguayo et al., 1990; Petronilho et al., 2007). Bombesin is also extensively produced by small cell lung cancer cells (Moody and Korman, 1988).

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The exact role of peripheral bombesin receptors in mediating respiratory reflexes is still poorly explored as well as the contribution of the vagal pathway. Therefore, the goals of the present study were 1) to determine the cardio-respiratory pattern elicited by an intravenous bombesin injection; 2) to evaluate the involvement of the lung vagi; and 3) to examine the contribution of specific bombesin receptors to the cardio-respiratory response.

Our rationale for using bombesin (frog peptide) rather than mammalian GRP was the much higher affinity of bombesin for both bombesin BB_1 and BB_2 receptors (4.5 and 13 times, respectively) compared with GRP (Jensen et al., 2008).

2. Materials and methods

2.1. Animals and surgical procedures

Ethical approval for the experimental procedures used in this study was obtained from the local institutional review committee. All animal procedures were in accordance with the NIH Guide for the Care and Use of Laboratory Animals. A total of 40 adult male Wistar rats weighing 200–250 g were anaesthetized with an intraperitoneal (i.p.) injection of 600 mg/kg urethane (Sigma) and 120 mg/kg alpha-chloralose (Fluka AG). The animals were placed in the supine position and they breathed spontaneously room air. The trachea was exposed in the neck, sectioned below the larynx and cannulated. Catheters were inserted into the femoral vein for drug administration and supplemental doses of anaesthetic and to the femoral artery for blood pressure monitoring. Rectal temperature was maintained close to 37–38 °C by a heating pad.

The midcervical vagi were bluntly dissected and prepared for bilateral vagotomy, prior to measuring the studied variables in neurally intact rats. They were measured again following section of the vagi to see whether peripheral input from the lung vagi contributes to the effects of bombesin. In the second experimental group of intact rats, bombesin was injected before and after pharmacological blockade with [D-Phe]^{12}-bombesin and BIM 23127.

2.2. Apparatus and measurements

Tidal volume signals were recorded with the pneumotachograph head attached to the tracheal cannula linked to Research Pneumotach System (RSS 100 HR, Hans Rudolph inc.) and a computerized recording system (Windows software version 3.07.02, KORR Medical Technologies Inc.) for measuring and recording respiratory frequency (f), tidal volume (V_T), respiratory minute volume (V_E), inspiratory (T_I) and expiratory (T_E) times and sighs. The electromyogram of the costal diaphragm was recorded with bipolar electrodes, amplified (NL 104, Digitimer), filtered and measured with a model AS 101 (Asbit) leaky integrator (time constant = 100 ms). Arterial blood pressure was measured with BP-2 blood pressure monitor (Columbus Instruments). The recordings were registered on an Omnilight 8M 36 apparatus (Honeywell). Sighs were defined as deep breaths characterized by 2–4 times larger tidal volume than normal, and a renewed inspiratory effort occurring towards the end of an otherwise-normal inspiration resulting in a longer duration of respiratory breath-sigh complex (Soltysik and Jelen, 2005).

2.3. Drugs

The drugs were prepared freshly from powder before each experiment. Bombesin (Tocris) was dissolved in distilled water and injected at a dose of 10 μg/kg as a bolus into the femoral vein. The dose of the drug used in our study was obtained from our preliminary dose-response experiments (Table 1), which showed that this dose resulted in maximum and uniform changes in tidal volume, respiratory rate and blood pressure in neurally intact rats (n = 20). [D-Phe]^{12}-bombesin (Tocris), a BB_1 and BB_2 receptor antagonist, and BIM 23127 (D-Nal-cyclo-[Cys-Tyr-D-TRP-Orn-Val-Cys]-2-Nal-NH_2, Tocris) a BB_1 receptor antagonist, were dissolved in distilled water and injected i.v. at a dose of 50 and 100 μg/kg, respectively. The optimal doses of the antagonists were derived from preliminary experiments (data not shown). Each drug bolus was immediately flushed with a 0.2 ml aliquot of saline.

2.4. Treatment schedule and groups

The cardiorespiratory effects were tested using single bombesin boluses, injected i.v. in the following experimental designs: (i) before and after bilateral midcervical vagotomy in otherwise intact rats (n = 7); (ii) before and after pharmacological blockade of BB_1 and BB_2 receptors by the antagonists, in intact rats (n = 13).

The baselines of each individual value of V_T, minute ventilation (V_E), respiratory rate (f) and mean arterial pressure were determined by averaging the variables measured for five respiratory cycles prior to and after the injection. The ventilatory data were derived from the integrated pneumotachograph signal just before bombesin injection, during the early post-bombesin phase, and at 30 s, 60 s, 2 min and 5 min after the challenge. The maximum post-bombesin change in V_T and f used for the comparison in dose-response and antagonists' study was the highest (tidal volume) or lowest (respiratory rate) mean value, chosen from the computed time points ranging from the early post-bombesin phase to 60 s. The number of sighs was counted during the first minute following bombesin administration.

2.5. Data analysis

The data on the bombesin dose effects on respiration were analyzed by one-way analysis of variance (ANOVA). All other experimental data were analyzed by repeated measures two-way ANOVA with time (pre-challenge and defined time points after challenge) and either innervation status (neurally intact and vagi cut) or antagonist pretreatment (yes or no) as a between condition factor. Differences between individual time points and experimental situations were evaluated by post-hoc Tuckey T-test. In all cases, $P<0.05$ was considered significant. All results shown are means ± S.E.M.

Table 1
Dose dependent effect of bombesin on tidal volume (V_T), frequency of breathing (f) and number of sighs (counted during the first 60 s after the challenge)

Dose μg/kg	Control	V_T (ml)	Increase in V_T (%)	Control	f (breaths/min)	Decrease in f (%)	Sighs (1/min)
		Max change			Max change		
1	1.54 ± 0.14	1.97 ± 0.3	28%	83.2 ± 2.1	82.6 ± 4.1	0.7%	3.0 ± 0.7
5	1.66 ± 0.16	2.6 ± 0.07[b]	57%	73.8 ± 4.2	67.0 ± 5.7	9.2%	6.4 ± 0.4[c, e]
10	1.44 ± 0.13	2.86 ± 0.4[a]	98%	78.0 ± 5.3	53.2 ± 6.9[b]	32%	8.6 ± 0.6[d]
25	1.4 ± 0.16	2.5 ± 0.44	79%	71.2 ± 8.9	52.6 ± 11.2[a]	26.1%	10.0 ± 0.8[d]

Maximum post-bombesin change in respiratory parameters expressed as means and as a percentage of increase in V_T and fall in f with reference to the baseline values. All values are means ± S.E.M., (n = 5). [a]$P<0.05$, [b]$P<0.01$ compared to the respective control value. [c]$P<0.05$, [d]$P<0.001$ comparing to the sigh number evoked with dose of 1 μg and [e]$P<0.01$ comparing to the sigh value evoked with dose of 25 μg.

3. Results

3.1. Dose-dependent effect of bombesin on respiration

The effects of intravenous injections of the different doses of bombesin on respiratory variables in the intact rats are shown in Table 1. All doses ranging from 1–25 μg/kg produced sighs and augmentation of tidal volume. Two lowest doses of 1 and 5 μg did not evoke significant changes in respiratory rate. The dose of 10 μg/kg appeared to be most effective in inducing profound changes both in tidal volume and frequency of breathing. The number of sighs occurring in the first minute after the challenge was similar to those elicited with the highest dose of 25 μg/kg. To carry out our study we chose the dose of 10 μg since the higher dose did not enhance the respiratory effects, prolonging only the time of recovery to the baseline (5 min).

The injection of an equal volume (0.2 ml) of the vehicle (distilled water) resulted in no respiratory and blood pressure change.

3.2. Cardio-respiratory effects of bombesin challenge in the intact and midcervically vagotomized rats

Fig. 1 illustrates a typical response to injection of bombesin (10 μg/kg) into the femoral vein in the neurally intact and subsequently vagotomized rat. Intravenous administration of bombesin in all 7 intact rats elicited sighs, increased V_T, decreased the frequency of breathing and produced hypertension. Respiratory effects induced by bombesin were completely abolished by the section of the midcervical vagi.

Two-way ANOVA showed an effect of bombesin challenge ($P=10^{-6}$) on tidal volume. In the neurally intact rats, V_T started to increase immediately after bombesin injection, reaching its maximum value at 30 s. The rise in V_T was maintained up to 2 min and at 5 min post-challenge returned to the control value (Fig. 2A). The section of midcervical vagi in itself increased the baseline value of tidal volume (ANOVA, $P=10^{-3}$) and prevented augmentation of V_T induced by bombesin before denervation (ANOVA, $P=10^{-5}$, Fig. 2A).

Bombesin produced a decrease in respiratory rate only in neurally intact animals (ANOVA, $P=10^{-4}$). This decrease was triggered promptly after bombesin injection and persisted for 2 min. Rats subjected to midcervical vagotomy had lower base level of the respiratory rate than control rats (ANOVA, $P=0.001$). As shown in Fig. 2B section of the vagi prevented the response to bombesin challenge (ANOVA, $P=10^{-4}$).

Minute ventilation was increased by the drug challenge (ANOVA, $P=10^{-3}$). The mean increase in V_E of the intact rats always resulted from the increased tidal volume. Maximal rise in V_E at 30 s post-bombesin was 148±7.7 ml min^{-1} compared with pre-drug level of 120±6.9 ml min^{-1} in the intact rats ($P=10^{-3}$). Following midcervical vagotomy, the mean value of V_E prior to bombesin was 102±6.8 ml min^{-1} and remained at 109±6.5 ml min^{-1} after the challenge ($P=0.94$) (data not shown).

Bombesin injection augmented the peak amplitude of the electromyogram (emg) of the costal diaphragm (ANOVA, $P=10^{-5}$). As illustrated in Fig. 2C an increase in the amplitude of the diaphragmatic emg was observed towards the end of bombesin injection and persisted elevated at 60 s post-challenge ($P<0.01$) in the intact animals only. Midcervical vagotomy significantly heightened the baseline value of the peak amplitude of emg (ANOVA, $P<0.05$), which showed no response to bombesin challenge.

Mean arterial pressure increased after bombesin challenge ($P=10^{-5}$, two-way ANOVA), attaining highest values at 15 s post-drug, and remained at the stable level over 5 min in the intact rats. Following vagotomy, the rise in mean arterial pressure was triggered at the same time point, but was higher between 30 s and 1 min ($P<0.05$), compared to pre-vagotomy response (Fig. 2D).

3.3. Ventilatory response to bombesin after pre-treatment with the antagonists

Two bombesin receptor antagonists: [D-Phe]^{12}-bombesin and BIM 23127 were tested separately to determine their ability to block bombesin-induced cardio-respiratory effects.

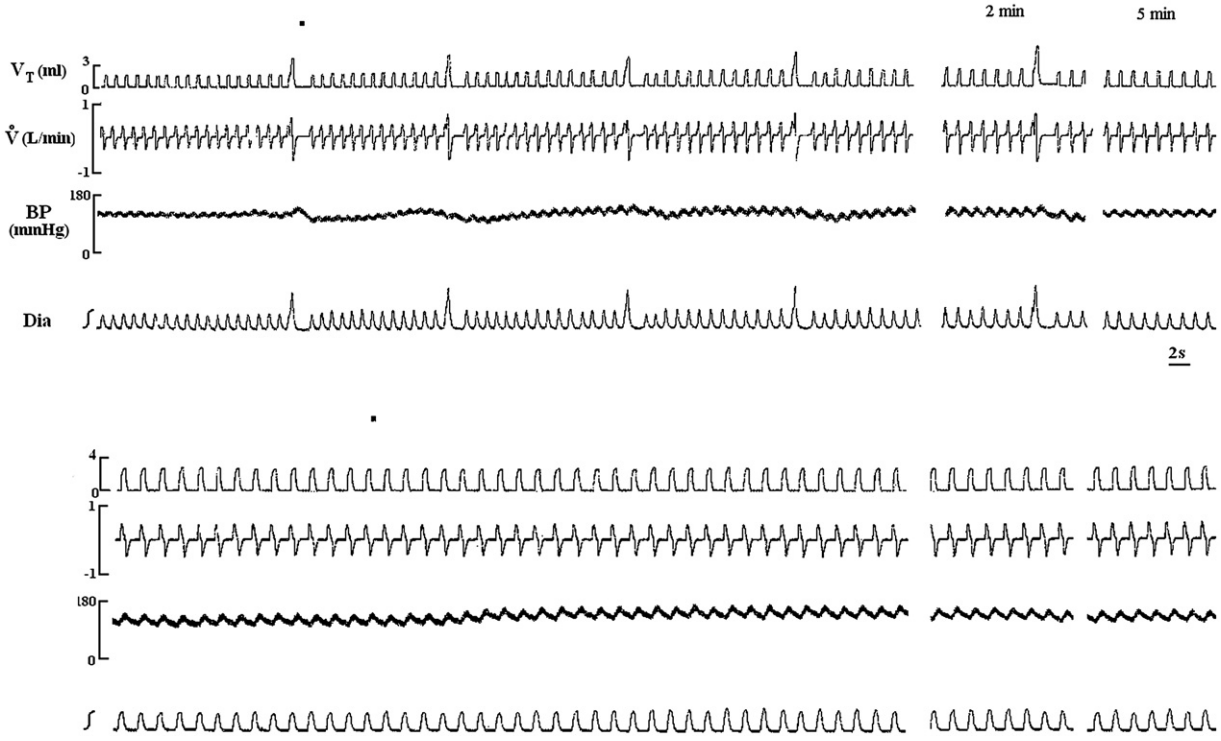

Fig. 1. A representative respiratory response pattern to i.v. administration of bombesin in a neurally intact rat (A) and after midcervical vagotomy (B). The injection time points are marked with dots above the upper trace. The dot signifies the end of drug injection. Note the sighs, decrease in the breathing rate coupled with augmentation of V_T and an increase in blood pressure in the intact state. V_T, tidal volume; $\dot{V}$, airflow; BP, blood pressure; ∫ Dia, electromyogram of the costal diaphragm.

The pretreatment with [D-Phe]^{12}-bombesin antagonist, which binds with equal affinity to the GRP (BB_2) and NMB (BB_1) receptor subtypes (Flynn, 1997), lowered the baseline values of the frequency of breathing ($P<0.05$) and increased arterial blood pressure (Fig. 3B, D). The time interval between the end of [D-Phe]^{12} injection and the subsequent administration of bombesin was 2 min. Blockade with this antagonist reduced the rise in tidal volume, the decrease in respiratory rate and hypertension formerly elicited by bombesin (Fig. 3A,B,D). After the blockade, the number of sighs was significantly diminished from the control value of 10±0.78 to 6.4±0.99 ($P<0.05$, $n=7$, Fig. 3C).

In the separate group of six rats, after application of BIM 23127, the selective BB_1 receptor antagonist, the cardiorespiratory responses to bombesin were left preserved. There was a similar rise in V_T and blood pressure, and the drops in f and the number of sighs were the same before and after the blockade (Fig 3A–D). Further increase in the dose of the antagonist was not effective. Doses higher than 100 μg affected the cardiorespiratory pattern by itself (data not shown).

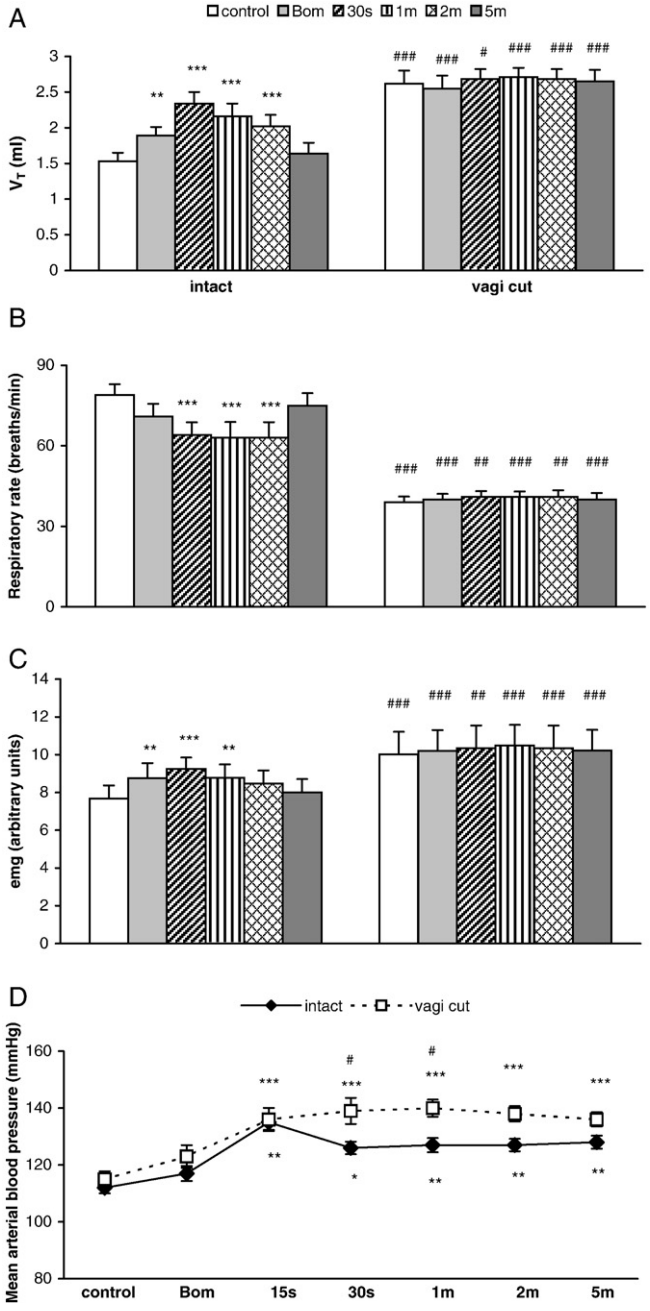

Fig. 2. Effects of i.v. administration of bombesin and section of the midcervical vagi on V_T (A), respiratory rate (B), amplitude of the peak height of emg (C) and blood pressure (D) in the intact rats ($n=7$). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, *versus* the respective pre-bombesin baseline value. $^{\#}P<0.05$, $^{\#\#}P<0.01$, $^{\#\#\#}P<0.001$, *versus* the corresponding pre-vagal section value.

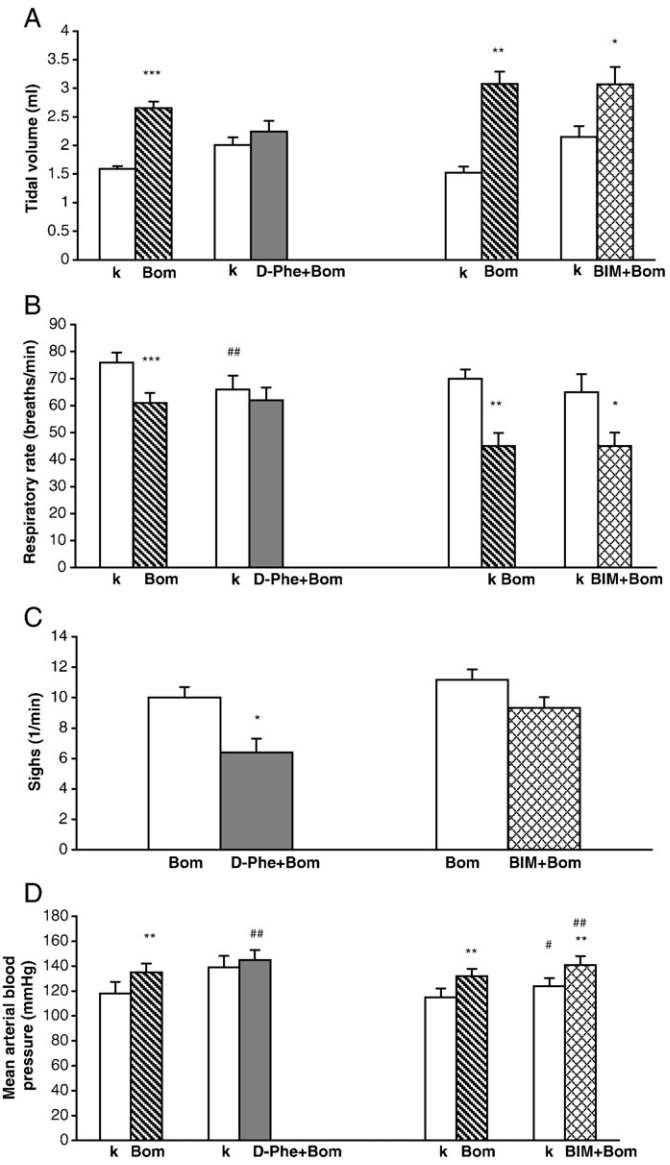

Fig. 3. Effect of bombesin BB_1 and BB_2 receptor blockade on post-bombesin changes in tidal volume (A), breathing rate (B), number of sighs (C) and mean arterial blood pressure in intact rats (D), ($n=13$). Note that [D-Phe]^{12} treatment prevented the increases in V_T, blood pressure and decreases in respiratory rate and reduced the number of sighs. $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, *versus* the respective pre-bombesin baseline value. $^{\#}P<0.05$, $^{\#\#}P<0.01$, *versus* the corresponding pre-antagonist baseline value.

4. Discussion

The present study has shown that in anaesthetized rats the predominant effect of an intravenous injection of bombesin was the occurrence of sighs, increase in tidal volume, decrease in breathing frequency and a rise in blood pressure.

The respiratory effects of peripheral bombesin administration are still poorly explored and the scant results are diverse. In cats, a ten times lower i.v. dose of bombesin than that used by us did not affect respiration (Holtman et al., 1983). In turn, an intravenous 2 min infusion of bombesin in rats was reported to produce rapid, shallow

breathing and hypotension (Gu and Lee, 2005). The dose applied by these authors was 1 μg/kg/min, whereas we used ten times higher dose, injected as a bolus. Nevertheless, even the comparably low dose of 1 μg/kg applied in our dose-effect relationship series consistently raised tidal volume and blood pressure, showing no effect on the breathing rate (Table 1). We cannot exclude the possibility that the discrepancy in the response was due to the different strains of rats (Sprague–Dawley) used in the quoted paper.

The post-bombesin increase in the arterial blood pressure was described in Wistar rats after bolus injection at a dose used in our study (10 μg/kg); unfortunately there were no data on the effects on respiration (Guarini et al., 1989).

The pattern of the respiratory response observed in the current experiments is consistent with some results obtained after central bombesin administration. The number of sighs induced by the dose of 10 μg/kg of neuropeptide given i.c.v. (Niewoehner et al., 1983), was comparable to that observed by us. Sighs are initiated by an inspiration-augmenting reflex arising in vagal afferents, probably from pulmonary irritant receptors (Głogowska et al., 1972). It is generally believed that they may serve to prevent atelectasis and are related to emotional states (Soltysik and Jelen, 2005). They are not observed as a part of normal respiratory pattern in anaesthetized rats (Niewoehner et al., 1983; and authors' own observations).

The effect on the breathing pattern, which we have found: an increase in V_T and decrease in f were in line with the results on intracerebroventricular application or microinjection of bombesin into the area of the nucleus ambiguus (Hedner et al., 1985). Yet, in contrast to the above-mentioned results, increases in f were described likewise after i.c.v. bombesin challenge (Niewoehner et al., 1983; Brown and Gillespie, 1988) and after microinjections into the area of nucleus tractus solitarii (Hedner et al., 1985). Regardless of the site of central injection, the only constant feature in most studies was the augmentation of tidal volume (Niewoehner et al., 1983; Hedner et al., 1985; Glazkova and Inyushkin, 2006).

It is generally held that peptides do not easily penetrate the blood–brain barrier (Prokai, 1998; Michaud et al., 1999) and there are no data on such an ability of bombesin.

At present we can rule out that the respiratory effects found in our experiments were due to the central action of bombesin. It is particularly suitable, when referring to our main finding, that midcervical vagal neurotomy eliminated all respiratory changes. This is consistent with the results of Gu and Lee (2005), who showed that perineural vagal block with capsaicin eliminated the respiratory contribution of bombesin in enhancing pulmonary chemoreflex. Since the pharmacological deafferentation technique elicits selective blockade of the C-fiber conduction in the vagus nerve, it suggests that nonmyelinated chemosensitive endings are involved in this response.

It is of note that previous studies implicated a contribution of the vagal mechanism in mediating the respiratory effects of bombesin. As reported by Hedner et al. (1985) cervical vagotomy eliminated central respiratory effects of the neuropeptide. It was further supported by the finding that atropine prevented the increase in f induced by i.c.v. injection of bombesin, indicating that peripheral cholinergic neurons in the vagus were involved in the response (Brown and Gillespie, 1988).

Although the expression of bombesin receptors on vagal pulmonary afferents has not yet been demonstrated, the presence of mRNA for all three subtypes of bombesin receptors was documented in airway epithelium of the mammalian lungs (Kane et al., 1996; Shan et al., 2004). Pulmonary epithelial neuroendocrine cells which, among other neuropeptides, release bombesin (Cutz et al., 2007), are innervated by the branches of sensory endings originating from the vagal nodose ganglia (Adriaensen et al., 1998; Brouns et al., 2003). Our finding supports the notion, that the vagal pathway is essential for the respiratory response to bombesin.

In the current experiments bombesin challenge stimulated diaphragmatic output by increasing its peak amplitude (Fig. 2C). This observation is consistent with the response of the diaphragm emg to microinjection of bombesin into nucleus tractus solitarii of rats (Glazkova and Inyushkin, 2006). Concomitantly enhanced tidal volume and diaphragm emg caused by an intravenous injection of bombesin in the present work were absent after elimination of phasic and tonic mechanoreceptor activity by vagotomy. It follows that the respiratory response to bombesin occurs with the interference of classically described positive feedback: lung vagi-phrenic motoneurons (DiMarco et al., 1981).

As mentioned in the Introduction, the respiratory effects of systemic bombesin challenge have not been studied and this applies to bombesin receptor antagonists. To verify if an increased post-bombesin ventilation and hypertension are caused by excitation of either receptor subtype: BB_1 (NMB-neuromedin B preferring) or BB_2 (GRP-preferring), we tested two classes of bombesin receptor antagonists. BIM 23127-selective BB_1 antagonist at a dose of 100 μg/kg was without effect in blocking the cardio-respiratory responses. In contrast to that, [D-Phe] ^{12}-bombesin (50 μg/kg), which binds with equal affinity to both BB_1 and BB_2 receptor subtypes (Flynn, 1997), significantly attenuated all respiratory changes and the increase in blood pressure (Fig. 3A–D). Taking also into account that bombesin binds with higher affinity to GRP-preferring receptor, our data implicate the involvement of BB_2 receptors in mediating cardio-respiratory neuropeptide effect.

In the current experiments bombesin caused a rise in blood pressure, independent of the lung vagal loop being closed or open. This observation confirmed the results of the earlier studies demonstrating a hypertensive response to central and systemic administration of bombesin (Guarini et al., 1989; Brown and Gillespie, 1988). The former was invariably present after vagal blockade with atropine, which indicates a non-vagal mechanism of bombesin action on blood pressure, supported by the results of the present work. In the current experiments the rise in blood pressure was smaller before vagotomy at 30 and 60 s. It was due to the occurrence of bombesin-induced sighs in the intact state, which probably caused small drops in the blood pressure.

The question arises as to why bombesin causes an increase in blood pressure. Guarini et al. (1989) attributed this increase in blood pressure to the release of an endogenous cholecystokinin induced by bombesin. Indeed, systemic administration of cholecystokinin at high doses was shown to increase arterial pressure in rats (Zhao et al., 2002). In this species, cholecystokinin-binding sites have been demonstrated within the vagus nerve, in nodose ganglia (displaying as well cholecystokinin-containing neurones) and in the nucleus tractus solitarii (Moran et al., 1990; Zhuo et al., 1997; Broberger et al., 2001). Therefore it is possible to speculate that cholecystokinin released in the nodose ganglia after injection of bombesin, transported to nucleus tractus solitarii (the first site of the reflex regulation of blood pressure) is involved in the observed hypertensive response, independent of the intact or damaged infranodose vagi. The mechanism underlying such effect remains, as yet, unclear. Moreover, there is little evidence that bombesin receptors are expressed in the nodose ganglia, apart from one report describing bombesin immunoreactivity in this structure in the crocodile (Karila et al., 1995). Nevertheless, the blockade of presumed bombesin receptors in our experiments with [D-Phe]^{12}-bombesin antagonist prevented the hypertensive response.

In conclusion, these data are the first to demonstrate that i.v. bombesin stimulates ventilation due to the occurrence of sighs and increase in tidal volume. The altered respiration is mediated via activation of BB_2 receptors inside the lung and mediated by the vagi, while the hypertensive response of the blood pressure occurs with the contribution of BB_2 receptors beyond the vagal loop.

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