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Neuromuscular blocking agents block carotid body neuronal nicotinic acetylcholine receptors

Malin Jonsson[a,*], Nicholas Wyon[b], Sten G.E. Lindahl[a], Bertil B. Fredholm[c], Lars I. Eriksson[a]

[a]*Department of Anesthesiology and Intensive Care Medicine, Karolinska Hospital and Institute, SE-171 76 Stockholm, Sweden*
[b]*Department of Anesthesiology and Intensive Care Medicine, University Hospital, Linköping, Sweden*
[c]*Department of Physiology and Pharmacology, Karolinska Institute, Stockholm, Sweden*

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Abstract

Neuromuscular blocking agents predominantly block muscle type nicotinic acetylcholine receptors as opposed to the neuronal type. However, there is growing evidence that neuromuscular blocking agents have affinity to some neuronal nicotinic acetylcholine receptors. The carotid body chemoreceptor as the essential oxygen-sensing cell, relies on cholinergic signalling. Atracurium and vecuronium impair carotid body chemoreceptor activity during hypoxia. Here, we characterize atracurium and vecuronium as antagonists at nicotinic receptors of the carotid body chemoreceptor. Isolated rabbit carotid body preparations with carotid sinus nerve were used, and chemoreceptor activities were recorded. There was a concentration-dependent reduction in the chemoreceptor responses to nicotine, with an IC_{50} to 50 μg nicotine of 3.64 and 1.64 μM and to 500 μg nicotine of 27.00 μM and 7.29 μM for atracurium and vecuronium, respectively. It is concluded that atracurium and vecuronium depress nicotine-induced chemoreceptor responses of the carotid body in a dose-dependent fashion.

Keywords: Carotid body; Nicotine; Atracurium; Vecuronium; Acetylcholine receptor; Anesthetic

1. Introduction

Since neuromuscular blocking agents were introduced into clinical practice in 1942, they have been extensively used in the practice of anesthesia and intensive care medicine. Synthetic muscle relaxants have developed by improving the selectivity muscle/ganglion, and are believed to have a low affinity to other acetylcholine receptors than the muscle type acetylcholine receptor (αβεδ) (Savarese et al., 1999). During recent years, however, studies performed on human neuronal nicotinic acetylcholine receptors expressed in *Xenopus* oocytes indicate that non-depolarising neuromuscular blocking agents have affinity to some neuronal nicotinic acetylcholine receptors (Chiodini et al., 2001; Garland et al., 1998). This subgroup of nicotinic acetylcholine receptors is present in the brain, peripheral ganglia, the adrenal medulla and the carotid bodies. Our group has previously shown that neuromuscular blocking agents decrease acute hypoxic ventilatory responses during iso- and poikilocapnia in human volunteers (Eriksson, 1996; Eriksson et al., 1992; Eriksson et al., 1993). Furthermore, the rabbit phrenic nerve output and carotid body chemoreceptor activity during hypoxia is reduced after close carotid body (Wyon et al., 1996) or systemic (Wyon et al., 1998) administration of a neuromuscular blocking agent. Later, it was shown that muscle relaxants partially block the in vitro carotid body response to hypoxia (Igarashi et al., 2002) and nicotine (Igarashi et al., 2002; Jonsson et al., 2002), confirming previous observations of the involvement of nicotinic acetylcholine receptors in carotid body chemosensation (Eyzaguirre and Monti-Bloch, 1982; Fitzgerald, 2000; Prabhakar, 2000).

The isolated rabbit in vitro carotid body preparation has previously been used to study carotid body chemoreceptor

* Corresponding author. Tel.: +46 8 51 77 20 66; fax: +46 8 30 77 95.
E-mail address: Malin.Jonsson@ks.se (M. Jonsson).

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signalling (Igarashi et al., 2002; Iturriaga et al., 1991; Iturriaga et al., 2000; Jonsson et al., 2002). Using this preparation, we applied concentrations of muscle relaxants based on data from previous studies using in vitro nerve-muscle preparations in rat (Fortier et al., 2001; Redai et al., 1995; Van der Spek et al., 1988). We hypothesize that the non-depolarising neuromuscular blocking agents atracurium and vecuronium depress nicotine-induced chemoreceptor responses in a dose-dependent manner and furthermore that equipotent neuromuscular blocking concentrations give rise to a similar degree of chemoreceptor depression.

2. Materials and methods

2.1. Animals and anesthesia

The study was approved by the Local Animal Care and Use Committee of the Karolinska Institute, Stockholm, Sweden. Experiments were performed on carotid bodies surgically removed from anesthetized male New Zealand White rabbits (n=26, weight 2750±250 g). Anesthesia was induced with thiopentone 50–60 mg i.v. given via a 24-gauge cannula in a left marginal ear vein. A continuous infusion of thiopentone was given at a rate of 90–180 mg kg^{-1} h^{-1} and adjusted to provide adequate surgical anesthesia. Muscle relaxants were not given to the animal. A tracheotomy was performed via an anterior midline incision after 5 ml of lidocaine to the skin (Xylocain® 5 mg/ml, AstraZeneca, Södertälje, Sweden). The animals were then mechanically normoventilated at a respiratory rate of 27 breaths/min using an animal ventilator (model 16/24, CF Palmer, London, UK) with a FiO_2 of 0.25–0.30.

2.2. Preparation of carotid bodies

The trachea and oesophagus were divided and retracted cranially to expose the carotid bifurcation on both sides. Under the microscope, the carotid sinus nerve and glossopharyngeal nerve were identified, carefully dissected and cut proximally to their confluence. The carotid artery was then identified and the animal was heparinised using 1500 IU heparin i.v. (Heparin Leo®, Leo Pharma, Helsingborg, Sweden). The carotid arteries were ligated and cut above the carotid bifurcation. The carotid body with its arterial supply and the carotid sinus nerve was then removed *en bloc*. The common carotid artery was flushed with a few milliliters of modified Tyrode's buffer solution before it was put into the perfusion chamber. All preparations were immediately used in the experiment. In the perfusion chamber, the common carotid artery was attached to a small plastic tube with a ligature and continuously perfused by gravity at a constant pressure height (45 cm of H_2O) with modified Tyrode's buffer solution equilibrated with 5% CO_2/95% O_2. The carotid body was also superfused via the chamber bath which received the same buffer as above via a separate plastic tubing. The volume of the chamber was approximately 2.5 ml, the exact volume depending on the size of the preparation placed in the chamber. The flow through the chamber was constant during each experiment ranging from 4 to 6 ml/min.

The composition of the modified Tyrode's buffer solution (mM) was 120.0 NaCl, 4.0 KCl, 2.0 $CaCl_2$, 1.0 $MgCl_2$, 21.4 $NaHCO_3$, 1.9 NaH_2PO_4, 10.0 D-glucose. The temperature of the perfusate was maintained at 37.0±0.5 °C by means of a regulated heating system (Heating Immersion Circulator, MP, Julabo, Germany). The buffer solution was equilibrated with 95% O_2 and 5% CO_2. Repeated samples were taken from the chamber and analysed (ABL 505, Radiometer, Copenhagen, Denmark) for pH, PO_2, PCO_2 and electrolyte content so as to ensure stable experimental conditions.

2.3. Carotid sinus nerve recording

In the perfusion chamber, the carotid sinus nerve was cut from the glossopharyngeal nerve and desheathed. The sinus nerve was placed onto a platinum electrode and covered by mineral oil to prevent drying. A reference electrode was placed in the tissue near the carotid body. Chemosensory discharges were recorded extracellularly from the whole carotid sinus nerve. The activity was amplified and filtered (100–10 kHz, notch filter 60 Hz) (A–M systems, differential AC amplifier model 1700, Carlsborg, WA, USA). The signal was then digitised and transferred onto a computer for continuous sampling and on-line analysis using a Digidata 1320A and pClamp 8 system (Axon Instruments, Foster City, CA, USA). As previously described (Iturriaga et al., 1991; Iturriaga et al., 2000), we used an electronic amplifier discriminator that allows selection of action potentials of a given amplitude above the baseline noise. The selected chemosensory impulses were counted with a frequency meter to measure f_x expressed in Hz. The response was defined as the peak chemoreceptor discharge frequency (f_x) compared to a baseline recording immediately prior to injection.

2.4. Dose–response relationship to nicotine in the isolated carotid body

Initially, a concentration–response relationship was established for nicotine by injection of 5–500 μg nicotine (nicotine hydrogen tartrate salt, Sigma Chemical, St. Louis, CO, USA) into the perfusate line with 20 min in between (Fig. 1A,B). Nicotine was dissolved in 0.5 ml of modified Tyrode's buffer and injected over 5 s into the perfusate as previously described (Jonsson et al., 2002). Based on this dose ranging (Fig. 1B), we chose doses of 50 and 500 μg nicotine for subsequent experiments (corresponding to peak concentration of approximately 36 μM and 360 μM, respectively). Injection of 0.5 ml of modified Tyrode's buffer solution did not result in any change of the chemoreceptor activity.

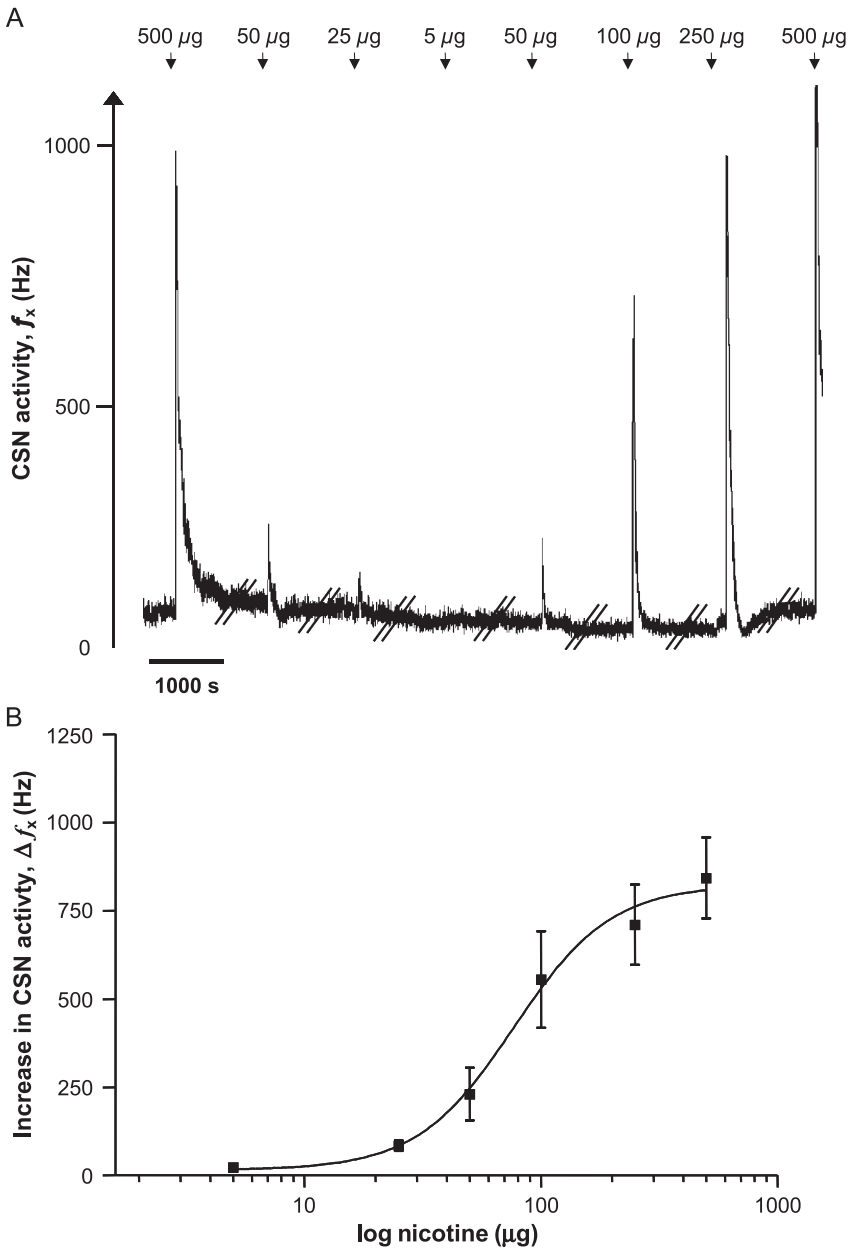

Fig. 1. (A) Recording of carotid sinus nerve (CSN) activity, f_x (Hz) in one carotid body preparation perfused with hyperoxic modified Tyrode's buffer solution. Arrows indicate administration of nicotine. Between each nicotine challenge, there was a 20-min washout period. (B) Dose-dependent increase in carotid sinus nerve (CSN) activity to nicotine (5–500 μg) in the isolated carotid body preparation. Hill slope: 2.12. Data are presented as mean±S.E.M. (n=4).

The chemoreceptor responsiveness and validity was confirmed for each preparation used by a 5–10-min standardized hypoxic test procedure (before and after the experimental procedure) using perfusate equilibrated with 5% CO_2/95% N_2 at normocapnia and a normal pH. The resultant increase in carotid sinus nerve activity was recorded and spike frequencies were compared before and after the end of the experimental protocol.

2.5. Nicotine-induced chemoreceptor responses

The 50-μg nicotinic challenges were studied in series of atracurium (Tracrium®, GlaxoSmithCline, Mölndal, Sweden) 0.28, 1.4, 2.8 or 5.6×10^{-6} M perfusate concentrations and vecuronium (Norcuron®, Organon, Gothenburg, Sweden) 0.1, 0.5, 1.0, 2.0×10^{-6} M perfusate concentrations. The 500-μg nicotine challenges were studied in series of atracurium 2.8, 5.6, 14.1 or 28.2×10^{-6} M and vecuronium 1, 2, 5 or 10×10^{-6} M perfusate concentrations. Following control responses, the four different concentrations of atracurium or vecuronium were tested, the order being rotated in which they where tested. After washout, nicotine 50 and 500 μg was administrated to verify the stability of the preparation.

The modified Tyrode's buffer solution as well as all drugs that were used during the experiment were prepared

the same day and kept in +4 °C. Atracurium was prepared immediately before use to avoid Hoffman degradation (Stiller et al., 1985). Doses were equipotent, assuming a dose potency ratio of 1:5 (Gramstad et al., 1983), which gives a concentration ratio of approximately 1: 2.8 between vecuronium and atracurium.

2.6. Statistical analysis

We applied off-line analysis of f_x before and after stimulation. Hence, absolute changes (Hz) in spike frequencies were calculated before and after exposure to nicotine and hypoxia and expressed as Δf_x=peak f_x−basal f_x. We normalized the data by construction of a ratio between the response after perfusion with muscle relaxants compared to the control response immediately before.

Concentration–response curves were adjusted using nonlinear regression and one site competition;

$$y = \text{Bottom} + (\text{top} - \text{bottom})/(1 + 10(x - \log IC_{50}))$$

where y is the chemoreceptor response expressed as a ratio. The IC_{50} was calculated using GraphPad Prism version 4.0 for Windows (GraphPad Software, San Diego, CA, USA). Significance was tested using Wilcoxon's signed rank test. Results are expressed as mean±S.D. A P-value of less than 0.05 was considered statistically significant.

3. Results

A total of 26 carotid body preparations were used to perform the experiments. Some of the preparations were used to test both atracurium and vecuronium. Baseline chemoreceptor frequencies (at hyperoxia) did not change during perfusion with any concentration of either atracurium or vecuronium.

The hypoxic response before and after the experiment was almost unchanged (in atracurium series 534±266 and 465±248 Hz (n.s.) and in vecuronium series 558±262 and 456±243 Hz, respectively (n.s.)).

We first examined the dose–response curve for nicotine (Fig. 1A,B). The data show that a half maximal response was obtained at 77 (95% C.I. 46–128) μg. Based on these findings, we examined the effects of two neuromuscular blocking agents at two doses, 50 μg which produced a response that was 27% of maximum and 500 μg, producing a maximal response.

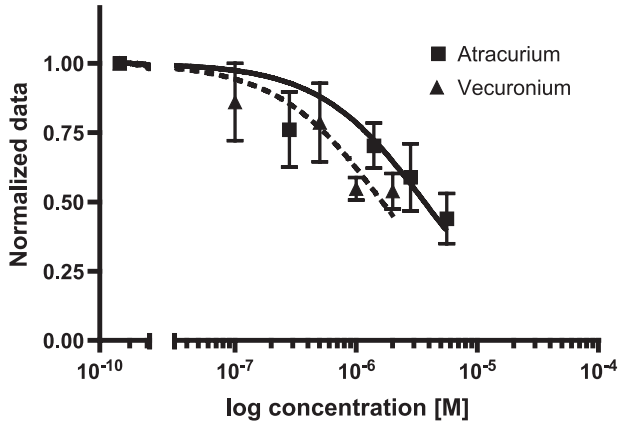

Fig. 2. Concentration-dependent blockade by atracurium and vecuronium on nicotine-induced carotid sinus nerve activity to 50 μg nicotine. The IC_{50} was 3.64 μM for atracurium and 1.64 μM for vecuronium. Normalized data (control/test response) are presented as mean±S.E.M. (n=5–7).

Table 1
Carotid body chemoreceptor responses to 50 μg nicotine

	Control before (Hz), mean±S.D.	Test (Hz), mean±S.D.	P-value, control vs. test	n
	Nicotine (50 μg)			
Atracurium series				
0.28 μM	346±324	301±322	n.s.	7
1.4 μM	320±306	233±307	<0.05	7
2.8 μM	301±304	216±277	<0.05	7
5.6 μM	368±324	168±155	<0.05	6
Control after test	325±303			8
Vecuronium series				
0.1 μM	419±217	347±236	n.s.	6
0.5 μM	393±232	215±203	n.s.	5
1 μM	432±229	242±121	<0.05	7
2 μM	314±180	174±102	<0.05	6
Control after test	368±257			7

Values are mean±S.D. The control value was compared with corresponding test value using Wilcoxon's signed rank test. A P-value of <0.05 was considered statistically significant.

Table 2
Carotid body chemoreceptor responses to 500 μg nicotine

	Control before (Hz), mean±S.D.	Test (Hz), mean±S.D.	P-value, control vs. test	n
	Nicotine (500 μg)			
Atracurium series				
2.8 μM	779±194	792±172	n.s.	6
5.6 μM	628±271	518±297	<0.01	11
14.1 μM	731±158	502±260	<0.05	7
28.2 μM	467±239	254±222	<0.05	7
Control after test	599±258			13
Vecuronium series				
1 μM	827±186	770±179	n.s.	6
2 μM	632±284	535±293	<0.01	11
5 μM	819±185	531±312	<0.05	6
10 μM	482±253	201±291	<0.05	6
Control after test	663±267			11

Values are mean±S.D. The control value was compared with corresponding test value using Wilcoxon's signed rank test. A P-value of <0.05 was considered statistically significant.

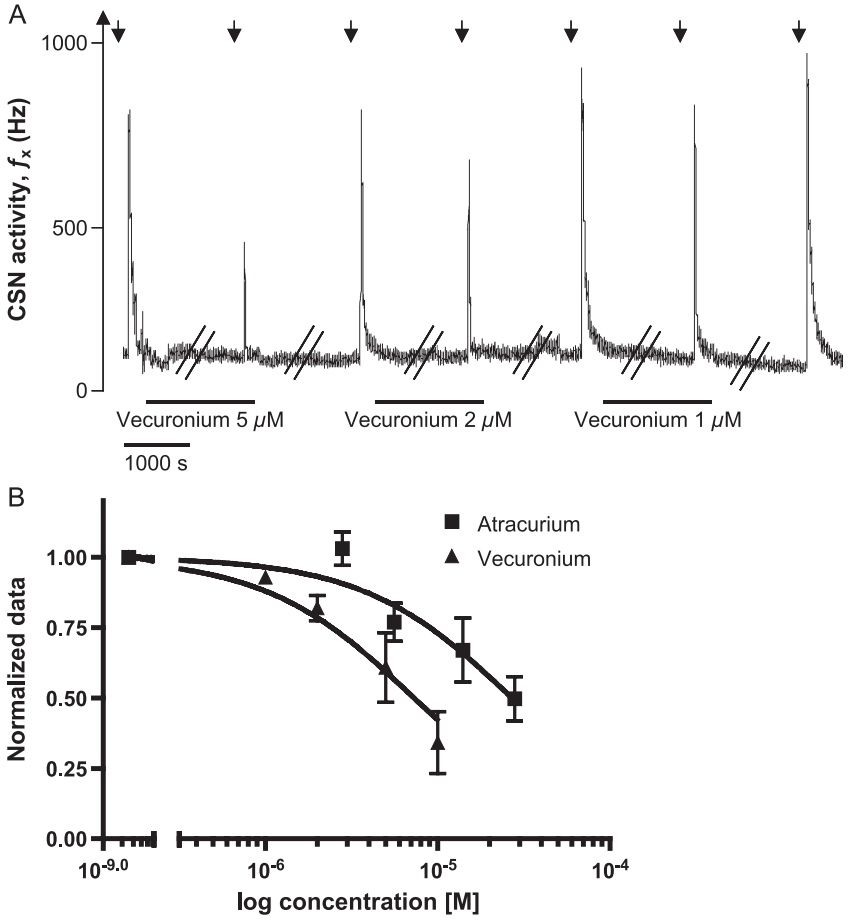

Fig. 3. (A) Recording of carotid sinus nerve (CSN) activity, f_x (Hz) in one carotid body preparation perfused with hyperoxic modified Tyrode's buffer solution. Solid bars represent 30-min perfusion with vecuronium 5, 2 or 1 μM. Arrows indicate injection of 500 μg nicotine. (B) Concentration-dependent blockade by atracurium and vecuronium on nicotine-induced carotid sinus nerve activity to 500 μg nicotine. The IC_{50} was 27.00 μM for atracurium and 7.29 μM for vecuronium. Normalized data (control/test response) are presented as mean±S.E.M. (n=6–11).

3.1. Effect of atracurium and vecuronium on nicotine-induced chemoreceptor responses to 50 μg nicotine

The absolute changes in chemoreceptor responses (Δf_x) in the atracurium and vecuronium series are presented in Table 1. As shown, there was a gradual reduction in nicotine-induced responses to increasing concentrations of the two neuromuscular blocking agents.

The resultant concentration–response relationships are presented in Fig. 2. Based on these relationships, the calculated IC_{50} was 3.64 (95% C.I. 2.22–6.05) and 1.64 (95% C.I. 1.05–2.57) μM for atracurium and vecuronium, respectively. This gives a concentration potency ratio (atracurium/vecuronium) of 1:2.22.

3.2. Effect of atracurium and vecuronium on nicotine-induced chemoreceptor responses to 500 μg nicotine

The absolute changes in chemoreceptor responses (Δf_x) in the atracurium and vecuronium series are presented in

Table 3
Analysis of samples taken from the perfusion chamber during the experimental period

	PO_2 (kPa)	PCO_2 (kPa)	pH	K (mmol/l)	Na (mmol/l)
Nicotine dose–response	69.82±6.31	4.88±0.29	7.35±0.02	3.9±0.04	136±0.9
Nicotine (50 μg)					
Atracurium series	69.69±4.14	4.63±0.29	7.36±0.03	3.9±0.04	137±1.9
Vecuronium series	69.69±5.81	4.66±0.32	7.36±0.03	3.9±0.04	137±2.4
Nicotine (500 μg)					
Atracurium series	64.61±6.06	4.49±0.44	7.38±0.05	3.9±0.04	135±1.6
Vecuronium series	63.34±5.68	4.41±0.30	7.38±0.03	3.9±0.06	136±2.0

Data are presented as mean±S.D.

Table 2. In these series, there was a marked reduction in nicotine-induced responses at increasing concentrations of the two neuromuscular blocking agents.

The resultant concentration–response relationships are presented in Fig. 3A,B. Fig. 3A shows an individual experiment in the atracurium series. Based on these relationships, the calculated IC_{50} was 27.00 (95% CI 18.07–40.33) and 7.29 (95% CI 5.13–10.37) μM for atracurium and vecuronium, respectively. This gives a concentration potency ratio (atracurium/vecuronium) of 1:3.70. In order to compare the data from the two doses of nicotine, we used a modification of the Cheng–Prusoff relationship: $IC_{50\text{-corr}}=IC_{50}(1/(1+dose_{nic}/IC_{50nic})$. Using this relationship, the results of the two series were quite comparable. Atracurium 2.2 and 3.6; vecuronium 1 and 0.98. Thus, the estimated potency ratio was 2.9.

Gas and electrolyte analysis from chamber perfusate samples (0.2 ml) were made at repeated 30-min intervals and are presented in Table 3.

4. Discussion

The main findings of this study were that (1) atracurium and vecuronium depress nicotine-induced carotid body chemoreceptor responses in a concentration-dependent fashion and (2) equipotent neuromuscular blocking doses of atracurium and vecuronium gave rise to a similar degree of depression of the chemoreceptor response, and finally (3) the IC_{50} ratio between atracurium and vecuronium was similar to those reported for neuromuscular blockade. Our findings suggest that two clinically used neuromuscular blocking agents block cholinergic transmission of the carotid body. Since the neuronal type nicotinic acetylcholine receptor are by far the most common cholinergic receptor type within the carotid body, our findings indicate that this block is due to an interaction with this receptor subtype.

In general, non-depolarising neuromuscular blocking agents are considered to have a low affinity to neuronal nicotinic acetylcholine receptors (Savarese et al., 1999). However, using human neuronal nicotinic acetylcholine receptor subtypes (α4β2, α3β4, α3β4α5 and α7) reconstituted in *Xenopus* oocytes, Chiodini et al. (2001) showed that atracurium and its degradation product laudanosine caused a marked concentration-dependent inhibition of these receptor subtypes with an IC_{50} in the micromolar range. Atracurium competitively blocked the major brain nicotinic acetylcholine receptor subtype α4β2 and the homomeric α7 subtype, while in a very low concentration, the α4β2 was activated (Chiodini et al., 2001). In addition, atracurium caused open channel block of the major peripheral nicotinic acetylcholine receptors α3β4 and α3β4α5 (Chiodini et al., 2001). Pancuronium and d-tubocurarine block the neuronal α4β2 nicotinic acetylcholine receptor expressed in the *Xenopus* oocyte (Garland et al., 1998). Based on this, we hypothesized that a similar block would occur in our isolated carotid body preparation using whole carotid sinus nerve recording.

The carotid body originates embryologicaly from the neural crest and consequently, carotid body nicotinic acetylcholine receptors are predominantly of the neuronal type. The neuronal nicotinic acetylcholine receptor subunit α4 has been demonstrated in the carotid body and the adjacent petrosal ganglion in cat (Ishizawa et al., 1996) and the α7 subunits have been found in the carotid body afferent system using immunocytochemical techniques (Ishizawa et al., 1996; Shirahata et al., 1998). In addition, α3, α4 and β2 subunits-containing nicotinic acetylcholine receptors are present and functional in cultured cat glomus cells (Higashi et al., 2003).

It is now accepted that detection of a low PO_2 in the carotid body involves inhibition of K^+-channels and a subsequent influx of extracellular calcium followed by transmitter release resulting in a discharge of the afferent carotid sinus nerve. In this context, acetylcholine has been found to be one of the most important transmitters in carotid body chemoreception (Fitzgerald, 2000; Prabhakar, 2000). In addition, α-bungarotoxin binding sites have been demonstrated on chemoreceptor type I cells (Chen et al., 1981; Dinger et al., 1981), and in vitro block achieved by d-tubocurarine results in hyperpolarisation of these cells (Eyzaguirre and Monti-Bloch, 1982).

Neuromuscular blocking agents have their preferred affinity to the muscle type nicotinic acetylcholine receptor at the neuromuscular junction, and their interaction with hypoxic ventilatory regulation has gone unnoticed until recently (Igarashi et al., 2002; Jonsson et al., 2002). A recent study has shown that vecuronium directly blocks hypoxic responses and nicotinic carotid body chemoreceptor responses in rat (Igarashi et al., 2002). Similar findings have been made for atracurium and vecuronium in the rabbit (Jonsson et al., 2002). Hence, we believe our findings support the hypothesis that the depression of the carotid body chemosensory response by muscle relaxants is due to a block of neuronal nicotinic acetylcholine receptors located in the carotid body. Since our experimental protocol tests both pre- and postsynaptic neurotransmission, our results provide no information as to whether this interaction is due to a pre- or postsynaptic (or both).

These data are in line with our previous results showing that muscle relaxants interfere with the hypoxic ventilatory response in humans, while leaving the hypercapnic ventilatory response unaffected (Eriksson, 1996; Eriksson et al., 1992; Eriksson et al., 1993). In the rabbit, a close carotid body injection of a minute dose of vecuronium reduces the hypoxic ventilatory response as shown by a reduction of phrenic nerve output during hypoxia (Wyon et al., 1996). This interference seems to emanate from a direct depression of carotid body chemoreceptor output (Wyon et al., 1998).

4.1. Critique of method

We have used a well-defined (Igarashi et al., 2002; Iturriaga et al., 1991; Iturriaga et al., 2000; Jonsson et al., 2002) isolated rabbit carotid body preparation to avoid systemic effects of nicotine administration and to study the action of muscle relaxants directly on the carotid body. Experiments were performed immediately after excision of the carotid body, which is crucial for the reliability of our results. We furthermore assured and documented a stable preparation as well as perfusate pH, PCO_2, PO_2, sodium and potassium, as measured at regular 30-min intervals during the whole experimental period (Table 3). Perfusate temperature and flow pressure were continuously assessed. The application of a constant perfusion flow governed by gravity via the carotid body arterial supply, made it possible to subtract coexisting baroreceptor activity, making it easier to interpret the variation in carotid sinus nerve impulse traffic as a reflection of chemosensation. We are aware that our carotid sinus nerve recording shows the entire nerve action where the quality of recording may vary over time due to recruitment or loss of additional carotid sinus nerve fibres. Therefore, for each concentration of muscle relaxant, we compared the change in chemoreceptor activity with the preceding control stimulation using their ratios. Between each perfusion period with muscle relaxant, a 20–30-min washout period was allowed, as well as subsequent nicotine injections to ensure and demonstrate stable experimental conditions over time. In addition, hypoxic tests were performed before and after each experiment to confirm the viability and stability of the carotid body chemosensitivity.

The nicotine doses were chosen after dose–response experiments so as to represent two parts of the dose–response curve (Fig. 1B). The atracurium and vecuronium concentrations were chosen to represent equipotent degrees of neuromuscular blockade (Gramstad et al., 1983). In order to avoid spontaneous degradation of atracurium to its metabolite laudanosine, we kept the solution in +4 °C before experiments. Despite this, we can expect a few percent of laudanosine in the atracurium solution. Therefore, it cannot be ruled out that the effect by atracurium was may partly caused by laudanosine, since laudanosine block nicotinic acetylcholine receptors (Chiodini et al., 2001) and furthermore can affect release of catecholamines (Kinjo et al., 1989).

It is impossible to do a direct extrapolation between clinical concentrations of muscle relaxants in humans to those used in animal in vitro preparations such as in this study because of species differences, possible in vivo–in vitro effects and difficulties to estimate the exact concentration in the target organ (Muir et al., 1989; Vizi et al., 2003). Data in rabbits are lacking and no comparison between rabbit and man can thus be made. Therefore, concentrations of atracurium and vecuronium used in this study were chosen after evaluation of the current information available from rat dose responses based on in vitro studies of nerve-muscle preparations (Fortier et al., 2001; Redai et al., 1995; Van der Spek et al., 1988). Interestingly, our IC_{50} for atracurium, 3.64 and 27.00 μM, and vecuronium, 1.64 and 7.29 μM, are similar to the EC_{50} found in such in vitro hemidiaphragm preparations (Fortier et al., 2001; Redai et al., 1995; Van der Spek et al., 1988). This in combination with a potency ratio at the same range as for the neuromuscular blocking effects strongly suggest that atracurium and vecuronium have an affinity to nicotinic acetylcholine receptors in the carotid body.

In contrast to the central nervous system, the periphery (e.g. peripheral ganglia, adrenal medulla and the carotid bodies) seem to be affected by muscle relaxants. The lack of effect within the central nervous system is based on the assumption that highly charged molecules only poorly pass the blood brain barrier. Recently, significant concentrations of atracurium but not vecuronium were detected in cerebrospinal fluid of patients during and immediately after intracranial aneurysm surgery (Tassonyi et al., 2002). In an earlier study, d-tubucurarine was found in human cerebrospinal fluid after a single intravenous dose (Matteo et al., 1977), and vecuronium was found in the cerebrospinal fluid of two patients with sepsis who were exposed to prolonged administration of vecuronium (Segredo et al., 1990). Therefore, in critically ill patients with a functional disruption of the blood–brain barrier neuromuscular blocking agents might enter the central nervous system and the interaction with neuronal nicotinic acetylcholine receptors may become clinically relevant.

Confirming our hypothesis, it is concluded that atracurium and vecuronium depress neuronal nicotinic acetylcholine receptors of the carotid body in a dose dependent fashion. The degree of depression is, at equipotent concentrations, similar between the two agents.

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