Effect of sugammadex on bronchial smooth muscle function in rats

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Abstract

Sugammadex can encapsulate the steroid-based neuromuscular blocker molecule and results in rapid reversal of neuromuscular blockade induced by rocuronium and vecuronium. However, several cases of bronchospasm after the administration of sugammadex have been reported. The current study was carried out to determine whether sugammadex directly affects smooth muscle function of the airways. The ring strips of left main bronchi were isolated from male Wistar rats and isometric forces were measured. In the isolated bronchial smooth muscle tissues, sugammadex (10^-8 – 10^-3 M) had no effect on baseline tension or the acetylcholine (ACh; 30 µM)-induced sustained contraction. Moreover, sugammadex did not affect bronchial smooth muscle responsiveness to ACh. These findings indicate that sugammadex itself does not affect contractile function in bronchial smooth muscle of the rat.

Key words: sugammadex, adverse effect, bronchial smooth muscle, rat

Introduction

In postoperative care, cholinesterase inhibitors such as neostigmine have been used for reversal of neuromuscular blockade induced by nondepolarizing neuromuscular blocking agents such as rocuronium and vecuronium. However, the cholinesterase inhibitors have several adverse effects including bradycardia, hypotension, and bronchospasm with autonomic instability.

Recently, sugammadex has been developed as a novel type of reversal agent and approved for clinical use in several countries. Sugammadex is a modified g-cyclodextrin with a hydrophobic cavity designed to encapsulate steroid-based neuromuscular blocking agents (Naguib, 2007), and is extremely effective when used for the reversal of rocuronium-induced neuromuscular blockade (Sparr et al., 2007). When administered intravenously, sugammadex is rapidly distributed to the effect component...
captures rocuronium, leading to a reduction of rocuronium concentration in the neuromuscular junctions.

The advantage of sugammadex for clinical use is the reversal of neuromuscular blockade without inhibition of cholinesterase. Inhibition of cholinesterase causes an increase in acetylcholine (ACh), occasionally resulting in bronchospasm via an activation of muscarinic receptors of the airways even in the non-asthmatic patients. Based on the mechanism of action, it is likely that sugammadex can avoid such adverse event. However, several cases of bronchospasm after administration of sugammadex have been reported (Amao, et al., 2007). In addition, the effect of sugammadex on airway smooth muscle is not fully understood. The current study was carried out to determine whether sugammadex directly affects smooth muscle function of the airways.

Methods

Male Wistar rats (10–12 weeks of age, 350–400 g) were purchased from Charles River Japan, Inc. (Kanagawa, Japan) and housed in a pathogen-free facility. All animal experiments were approved by the Animal Care Committee of Kawasaki Medical School (Okayama, Japan).

The isometric contraction of the left main bronchial ring was measured as previously described (Chiba et al., 1999; 2008; Hanazaki et al., 2008). In brief, rats were sacrificed by exsanguination from abdominal aorta under inhalation of sevoflurane (5%, Maruishi Pharmaceutical. Osaka, Japan) anesthesia. After thoracotomy, a 3-mm length of the left main bronchus was isolated, and the resultant tissue ring preparation was suspended in a 10-mL organ bath at a resting tension of 1 g. The isometric contraction of the circular smooth muscle was measured with a force-displacement transducer (T7-8-240, Orientec, Japan). The organ bath contained modified Krebs–Henseleit solution with the following composition (mM); NaCl 118.0, KCl 4.8, CaCl 2 2.5, MgSO 4 1.2, NaHCO 3 25.0, KH 2PO 4 1.2 and glucose 11.0 (pH 7.4). The buffer solution was oxygenated with 95% O 2–5% CO 2 at room temperature. During an equilibration period in the organ bath, the tissues were washed three or four times at 15 min intervals and were equilibrated slowly to a baseline tension of 1 g. After the equilibration period, effects of sugammadex sodium (MSD K.K., Japan) on baseline tension and ACh-induced contraction were evaluated.

All the data are expressed as the mean ± S.D. Statistical significance of difference was determined by unpaired Student’s t-test or two-way analysis of variance (ANOVA) with post hoc Bonferroni/Dunn. A value of P<0.05 was considered significant.

Results

Effect of sugammadex on baseline tension

To determine whether sugammadex has an ability to induce bronchial smooth muscle contraction, sugammadex (10⁻⁸ – 10⁻³ M) was administered cumulatively. As shown in Fig. 1, sugammadex had no effect on baseline tension of the rat bronchial smooth muscles even at the highest concentration.
Sugammadex does not affect BSM function

Effect of sugammadex on submaximal contraction induced by ACh

In another preparations of the bronchial rings, 30 µM ACh, which produced approximately 50% of the maximal ACh-induced contraction (Hanazaki et al., 2008), was applied to the tissues after the
equilibration period. When a stable contraction with 30 µM ACh was observed, sugammadex (10 and 100 µM) was administered cumulatively. As shown in Fig. 2, neither an augmentation of the contraction nor relaxation was produced by sugammadex.

Effect of sugammadex on bronchial smooth muscle responsiveness to ACh

In another series of experiments, to determine whether sugammadex augments bronchial smooth muscle responsiveness to ACh, the concentration-response curves to ACh ($10^{-7} - 10^{-3}$ M) were constructed cumulatively in the same preparations in the absence and presence of sugammadex (10 µM). Sugammadex was administered 5 min before application of the first concentration of ACh ($10^{-7}$ M). Each point represents the mean ± S.D. from 6 animals. No statistically significant difference was observed between the groups.

Discussion

To determine whether sugammadex directly affects smooth muscle function of the airways, the agent was applied directly to the isolated bronchial smooth muscle of rats. As results, sugammadex had no effect on baseline tension (Fig. 1) or the ACh-induced sustained submaximal contraction (Fig. 2). In addition, the bronchial smooth muscle responsiveness to ACh was not affected by the in vitro pretreatment with sugammadex (Fig. 3). These findings indicate that sugammadex itself does not affect
contractile function of bronchial smooth muscle in the rat.

Sugammadex has been used for reversal of neuromuscular blockade induced by rocuronium and other steroid-based neuromuscular blocking agents. The mode of action of sugammadex is unique like a chelation effect (Naguib, 2007). Clinical studies in healthy volunteers and patients indicate that sugammadex is well tolerated, but some adverse effects have also been reported. One of the critical adverse effects is bronchospasm. Amao and colleagues (2007) reported that 2 of the 77 patients with pulmonary disease caused bronchospasm after the administration of sugammadex. Although the mechanism of bronchospasm induced by sugammadex is unclear, both patients had a history of asthma (Amao et al., 2007), indicating that the bronchial smooth muscle hyperresponsiveness, one of the features of asthmatics (Martin et al., 2000; Seow et al., 1998), might be involved in. Sugammadex itself may have caused bronchial smooth muscle contraction in these patients. On the other hand, in one of the 2 patients, the bronchospasm was observed about 1 hr after the administration of sugammadex (Amao et al., 2007). In this case, the delayed response indicates that the sugammadex-rocuronium clathrate complex generated after the intravenous administration of sugammadex may have caused bronchial smooth muscle contraction. Alternatively, factor(s) other than bronchial smooth muscle, such as stimulation of cholinergic nerves, activation of mast cells, and so on, might be involved in the in vivo bronchospasm induced by sugammadex and/or the sugammadex-rocuronium clathrates. For its safer clinical use, further studies are needed to make clear the mechanism of bronchospasm induced by sugammadex.

In conclusion, the present study clearly demonstrated that, at least in normal rats, sugammadex itself has no effect on the function of the isolated bronchial smooth muscle.

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References


