Anaphylaxis to sugammadex-rocuronium inclusion complex : an IgE-mediated reaction due to allergenic changes at the sugammadex primary rim

Anaphylaxis to sugammadex-rocuronium inclusion complex: an IgE-mediated reaction due to allergenic changes at the sugammadex primary rim.

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*Short title: "***Anaphylaxis to the sugammadex-rocuronium inclusion complex***"*

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Key words: anaphylaxis, basophil activation, IgE, rocuronium, sugammadex, sugammadex-rocuronium inclusion complex (S-R-Cx), allergenicity of sugammadex-rocuronium complex;

Clinical implications

We describe a patient who experienced IgE/FcεRI-dependent anaphylaxis to the S-R-Cx rather than each agent in separation and in whom the anti-S-R-Cx IgE antibodies might involve shape alterations of the carboxy-ethyl side-chains attached at the primary rim of sugammadex**.**

The aminosteroids rocuronium, vecuronium, pancuronium and pipecuronium are neuromuscular blocking agents (NMBAs) with a four-ring androstane nucleus substituted at position 2 and 16 producing monoquaternary or bisquaternary compounds (Repository Figure E1 and Table E1). These tertiary and quaternary substituted ammonium structures can bind with NMBA-reactive sIgE antibodies (sIgE) [1]. Sugammadex is a modified γ-cyclodextrin designed as a selective relaxant-binding agent (SRBA), by encapsulating and forming high affinity complexes with steroidal NMBAs, particularly rocuronium [2]. When rocuronium is complexed with sugammadex forming the inclusion complex (S-R-Cx), the N-allylpyrrolidinium quaternary ammonium group is visible at the primary rim surrounded by the thio(2-carboxyethyl)sodium groups while its polar 2-morpholino and 3-OH groups protrude slightly from the secondary rim of the S-R-Cx [3] (Figure 1a, 1b). This suggests that the potentially allergenic ammonium groups of rocuronium might still be accessible for binding to complementary sIgE antibodies [4]. Although there are several reports on IgE-mediated anaphylaxis to sugammadex, hypersensitivity to the S-R-Cx is rare [5-7]. In these cases skin tests (ST) were negative for rocuronium and sugammadex individually and positive for the S-R-Cx.

A 63-year-old woman attended our outpatients' clinic because of anaphylaxis after surgery for sigmoid carcinoma. Induction of anaesthesia (14h55) included sufentanil 15 µg, propofol 200 mg, rocuronium 80 mg and sevoflurane. She received clindamycin and metronidazole as antibiotic prophylaxis. Because of abdominal tension, she had an additional bolus of rocuronium (20 mg). Surgery was completed uneventfully (16h50). At that time, objective neuromuscular monitoring (Train of Four) was used to determine neuromuscular transmission. Once deep block had spontaneously recovered to moderate block, sugammadex 50 mg was administered. After extubation (17h00), she was transferred to the recovery room, where she arrived in good condition. Around 17h25, cyanosis (saturation of 72%), sinus bradycardia 52/min and no palpable pulse (54/25mmHg) were noticed and CPR was started. Tracheal intubation was performed without difficulty. After eight minutes of advanced life support, return of spontaneous circulation (ROSC) was achieved, (cumulative dose of adrenaline 4mg IV). After ROSC, an infusion of noradrenaline was started (0.25 µg/kg/h) and she was transferred to intensive care. Immediately after resuscitation, a diffuse erythema and slight facial oedema became apparent. Corticoids and antihistamines were administered. Noradrenaline was tapered and stopped in the following hours. The patient was extubated three days later. Serum tryptase taken 1.5 hour after onset of the reaction was 91.5 µg/L, baseline tryptase 5.2 µg/L, indicating mast cell activation. History revealed a non-confirmed penicillin allergy. She never had general anaesthesia before and denied intake of the opiate antitussive pholcodine. Total IgE and sIgE to latex, chlorhexidine, suxamethonium, rocuronium and morphine (ImmunoCAP Phadia TFS, Uppsala, Sweden) were quantified. Results $\geq$ 0.35 kUA/L were considered positive, except for suxamethonium and rocuronium for which thresholds

were set at 0.13 kUA/L and 0.11 kUA/L, respectively. SIgEs were 6.08 kUA/L for suxamethonium, 0.22 kUA/L for rocuronium and 1.23 kUA/L for morphine, indicating a sensitization to substituted ammonium structures. SIgE to chlorhexidine and latex was negative. Total IgE was 735 kU/L.

Skin prick tests (SPT) and intradermal tests (IDT) included propofol (10mg/mL, IDT 1:10), sufentanil (5µg/mL, IDT 1:10), rocuronium (10mg/mL, IDT 1:200), clindamycin (150mg/mL, IDT 1:10), metronidazole (5mg/mL, IDT 1:10), sugammadex (100mg/mL, IDT 1:10), latex (Lofarma, Italy) and chlorhexidine 5% (IDT 1:1000). ST were negative up to the concentrations indicated. Provocation tests with lidocaine and bupivacaine (1 mL of neat solution) were negative.

Because of the temporal relationship between the administration of sugammadex and negative ST to the SRBA, ST with the S-R-Cx were performed. Four mixtures of the S-R-Cx were prepared, i.e., sugammadex 367 µM + rocuronium 328 µM (367/328 µM); sugammadex 36.7 µM + rocuronium 32.8 µM (36.7/32.8 µM); sugammadex 3.67 µM + rocuronium 3.28 µM (3.67/3.28 µM); and sugammadex 0.367 µM + rocuronium 0.328 µM (0.367/0.328 µM). IDT with S-R-Cx 36.7/32.8 µM yielded a wheal/ flare of 7/15 mm. IDT with S-R-Cx 36.7/32.8 µM proved negative in five healthy controls and also five suxamethonium allergic patients.

As shown in figure 2a, BAT with rocuroniumand sugammadex proved negative. In contrast, the S-R-Cx triggered an appearance of CD63 in up to 25% of cells for the 36.7/32.8 µM formulation. BAT with the S-R-Cx in healthy controls and suxamethonium allergic patients remained negative (not shown).

To explore the clinical significance of her sensitization to substituted ammonium structures, additional investigations were performed. ST being unreliable for morphine, this opiate was examined in the BAT that proved negative (not shown). A provocation with morphine (cumulative dose 11 mg) was uneventful.

Suxamethonium (Celocurine®, CSP Benelux, 10mg/mL, 1:5) triggered a positive SPT (wheal/flare: 7/12mm) and a positive BAT (345 µM, 13% $CD63^{+ve}$ cells), indicating a clinical relevant sensitization.. For cisatracurium (Nimbex®, 2mg/mL, Aspen), ST and BAT were negative, indicating cisatracurium to be safe for future anaesthesia.

To study how the formation of the S-R-Cx can lead to changed allergenic properties relative to the free host (sugammadex) and guest (rocuronium) compounds in a patient not sensitized to the individual drugs, a series of BAT were undertaken. As shown in figure 2b, the phosphoinositide (PI) 3-kinase inhibitor, wortmannin, inhibited basophil responses to anti-IgE and the S-R-Cx but not to fMLP. Suggesting anaphylaxis to the S-R-Cx to be IgE/FcεRI-dependent [8].

Results of BAT with 2-hydroxypropyl-β-cyclodextrin and 2-hydroxypropyl-γ-cyclodextrin (825, 4792 and 40,603 μM), complexed with rocuronium (3.28, 32.8 and 328 μM) proved negative (not shown), suggesting that the reaction is likely to be specific for sugammadex.

To study the antibody recognition structure of the S-R-Cx, rocuronium was substituted by other steroidal NMBAs and a rocuronium analog 2β,3α,5α,16β,17β)-17-acetoxy-3-hydroxy-2-(4-morpholinyl)-16-(1-pyrrolidinyl)androstane (henceforth termed desallyl rocuronium) that has a pyrrolidinium instead of, like rocuronium, a positively charged quaternary ammonium N-allylpyrrolidinium group at position 16. The steroid antibiotic fusidic acid that lacks both the quaternary substituted ammonium group at position 16 and the morpholino group at position 2 was studied as it forms complexes with sugammadex [9]. As shown in figure 2c, the BAT with complexes of sugammadex and NMBAs and desallyl rocuronium were all positive. Complexes with fusidic acid, the free steroidal NMBAs and desallyl rocuronium, were inactive in the BAT (not shown).

This case report has several implications. Firstly, it emphasizes that the S-R-Cx could trigger anaphylaxis in patients demonstrating negative ST and BAT to the NMBA and the SRBA. Therefore, the diagnostic exploration of such a patient, would not be appropriate if it failed to test for the S-R-Cx. Secondly, we show that BAT could document anaphylaxis to S-R-Cx and benefit elucidation of the uncertainties associated with ST for the S-R-Cx. Thirdly, the BAT could enable exploration of cross-reactivity with other sugammadex-containing complexes and might help to explain how complex formation might alter allergenic properties of the constituent molecules and trigger effector cell degranulation.

BAT show that the reaction in our patient could be IgE/FcεRI-dependent and provoked by the S-R-Cx. This sensitization is not specific for rocuronium but specific for the γ-cyclodextrin sugammadex, since the 2-hydroxypropyl-β-cyclodextrin and 2-hydroxypropyl-γ-cyclodextrin complexes were BAT-negative..

In trying to explain the antibody recognition of the S-R-Cx, the possibilities appear to be due to an effect at the primary and/or secondary end of the S-R-Cx. To explore these possibilities, rocuronium was substituted by other steroidal NMBAs, desallyl rocuronium and the steroid fusidic acid. Results suggest that antibody recognition is independent of the NMBA and is unlikely to involve the steroid backbone since the response to fusidic acid-sugammadex complex was negative.

Although the models and structure-activity findings considered here suggest antibody recognition of the primary end of the S-R-Cx, confirmation of lack of recognition of the secondary end of the complex would require experiments with an analog with a morpholino group at position 2 and a hydroxyl at position 3 and no tertiary or quaternary ammonium group at position 16. However, there are no examples of analogs that might provide the definitive answers we are seeking at the secondary rim.

Finally, based on the positive BAT with the tertiary ammonium rocuronium analog, desallyl rocuronium, it seems that the positively charged quaternary ammonium ion located at the primary rim of the sugammadex cone is not essential for IgE recognition of the complex. We hypothesise that the guest perturbs or distorts the sugammadex structure, giving rise to a shape change and new structural features absent on sugammadex and this new or altered determinant is recognised by serum sIgE antibodies of some patients. Since the sugammadex cone is rigid, these shape perturbations are likely to involve the carboxy-ethyl side-chains attached via a sulphur atom to the primary rim and to result from electrostatic and van der Waals forces that contribute to binding of the guest to the host.

We describe a patient who experienced anaphylaxis to the S-R-Cx in whom the anti-S-R-Cx IgE antibodies recognise the complex regardless of the individual steroidal NMBA and regardless of charge. This IgE recognition is likely to involve shape alterations of the carboxy-ethyl side-chains attached at the primary rim of sugammadex. As these changes are not specific for rocuronium, use of sugammadex as a SRBA for other steroidal NMBAs is excluded.

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Figure legends

Figure 1: Corey-Pauling-Koltun (CPK) molecular models of sugammadex, rocuronium, the rocuronium analog (allyl group of rocuronium missing), and the host-guest complexes of rocuronium and its analog each with sugammadex. (a) Conventional colours for atoms. Rocuronium (middle structure) reacts with sugammadex (left structure) forming the sugammadex-rocuronium inclusion complex. (b) Colouring changed to distinguish the rocuronium structure from sugammadex. Pyrrolidinium group of rocuronium coloured brown; allyl group green; rest of rocuronium molecule purple. Note small parts of the rocuronium structure visible at both the primary and secondary ends of the inclusion complex. (c) Conventional colours for atoms. Rocuronium analog, desallyl rocuronium, (middle structure) reacts with sugammadex (left structure) forming desallyl rocuronium-sugammadex inclusion complex. (d) As for (b) but showing formation of rocuronium analog-sugammadex inclusion complex. Again, there are glimpses of the guest molecule at both ends of the host. In (a) and (c) the atoms are shown in their conventional colours, i.e., H white, C black, O red, N blue, S yellow, Na purple.

Figure 2a: Basophil activation plots in the patient for rocuronium, sugammadex and the sugammadex-rocuronium complex. Selection of basophils as IgE+CD203c+ cells. Stimulation with buffer does not induce up-regulation of CD203c nor CD63. For rocuronium and its reversal drug sugammadex, no basophil responsiveness is demonstrable. In contrast, the sugammadex-rocuronium inclusion complex (S-R-Cx) triggers a significant activation and degranulation, as is reflected by the up-regulation of CD203c and the lysosomal marker CD63. Similar basophil activation experiments in five healthy control individuals and five suxamethonium allergic patients remained entirely negative (appearance of CD63 <5%, data not shown).

Figure 2b: Basophil activation plots in the patient for stimulation with the positive control anti-IgE (aIgE), fMLP and the sugammadex-rocuronium complex (S-R-Cx) without (a, c, e) and with the phosphoinositide (PI) 3-kinase inhibitor wortmannin (b, d, f). Wortmannin 0.1 µM inhibits basophil responses to anti-IgE and the S-R-Cx but not to fMLP.

Figure 2c: Basophil activation plots in the patient for complexes with vecuronium (S-V-Cx), pancuronium (S-Pa-Cx), pipecuronium (S-Pi-Cx) and the rocuronium analog (S-Ra-Cx), desallyl rocuronium (2β,3α,5α,16β,17β)-17-acetoxy-3-hydroxy-2-(4-morpholinyl)-16-(1-pyrrolidinyl)androstane). BAT with all these complexes are positive.

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Figure E1: Structures of steroidal neuromuscular blocking agents (NMBAs) rocuronium, vecuronium, pipecuronium and pancuronium, desallyl rocuronium and the antiseptic fusidic acid. In rocuronium the numbered androstane nucleus that is used for all steroidal NMBA is shown in red. The rocuronium analog, desallyl rocuronium (2β,3α,5α,16β,17β)-17-acetoxy-3-hydroxy-2-(4-morpholinyl)-16-(1-pyrrolidinyl)androstane), has a tertiary pyrrolidinium group at position 16 instead of the quaternary positively charged N-allyl-pyrrolidinium group of rocuronium. For further information on the structures of NMBAs the reader is referred elsewhere [1]. Note that the four-ring androstane nucleus substituted at position 2 and 16 producing monoquaternary or bisquaternary compounds. These tertiary and quaternary substituted ammonium structures can bind with NMBA-reactive sIgE antibodies (sIgE) [1-3].

Table E1: substitutions at positions 2, 3, 16 and 17 for steroidal neuromuscular blocking agents (NMBAs)

Confirmatory testing and interpretation thereof

With respect to confirmatory in vitro and skin tests see [3] for sIgE NMBA, [4] for skin testing and [5-7] for basophil activation tests (BAT). Mast cell activation was defined as acute tryptase exceeding 1.2xbaseline + 2 µg/L [8].

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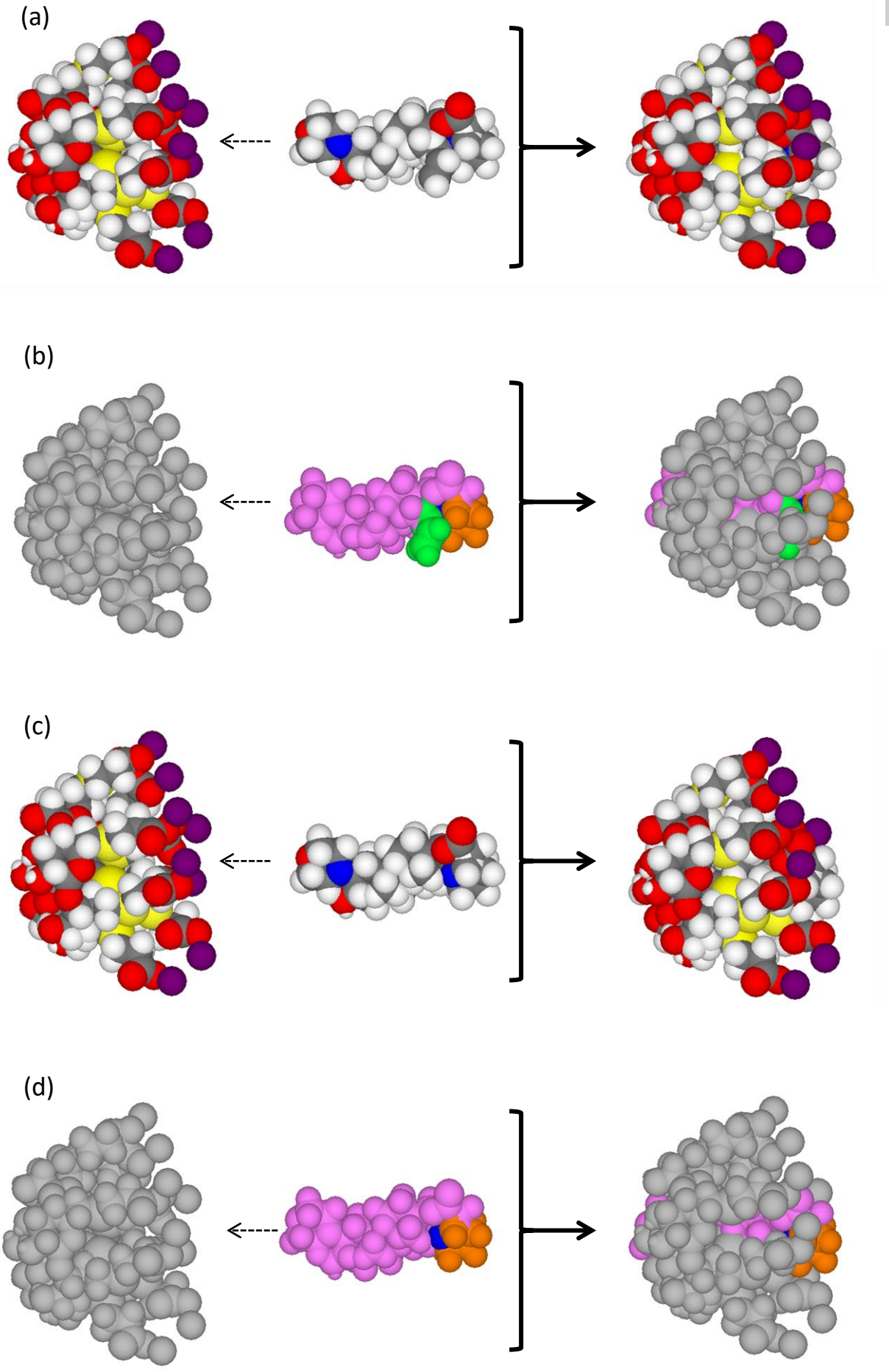
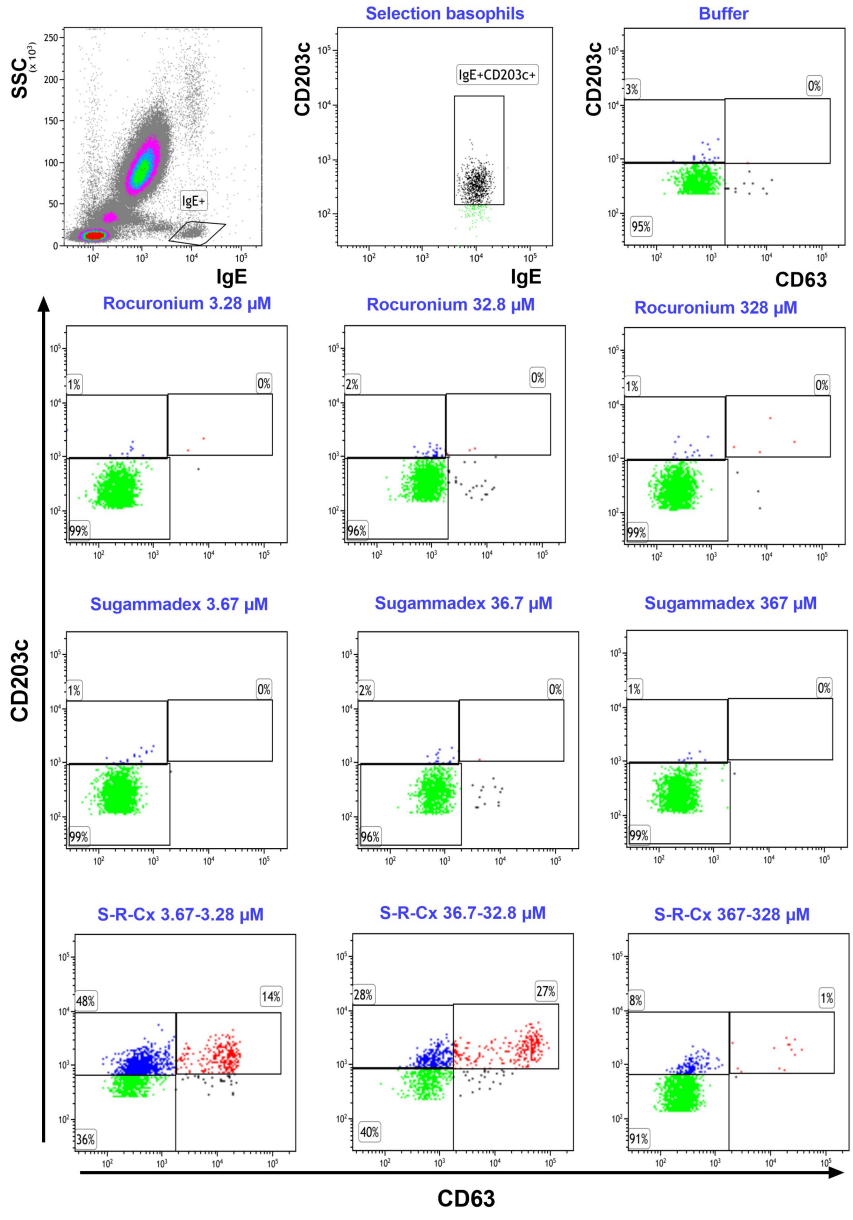
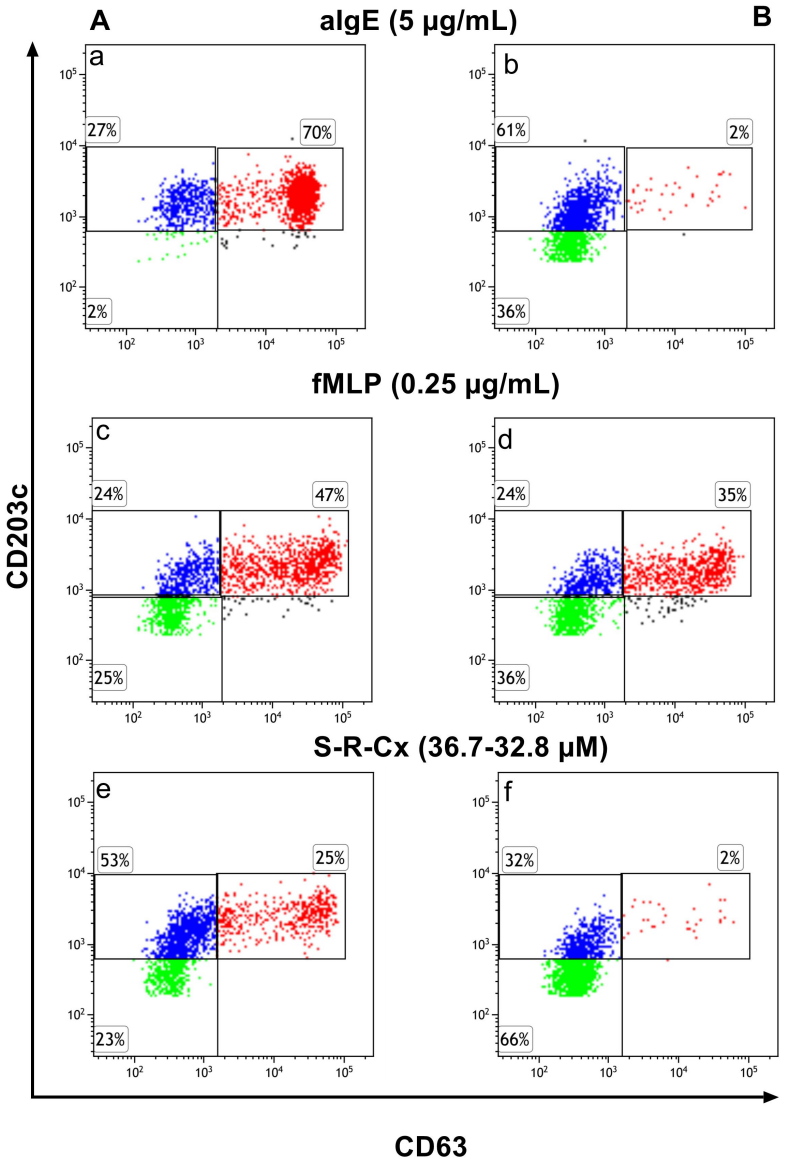
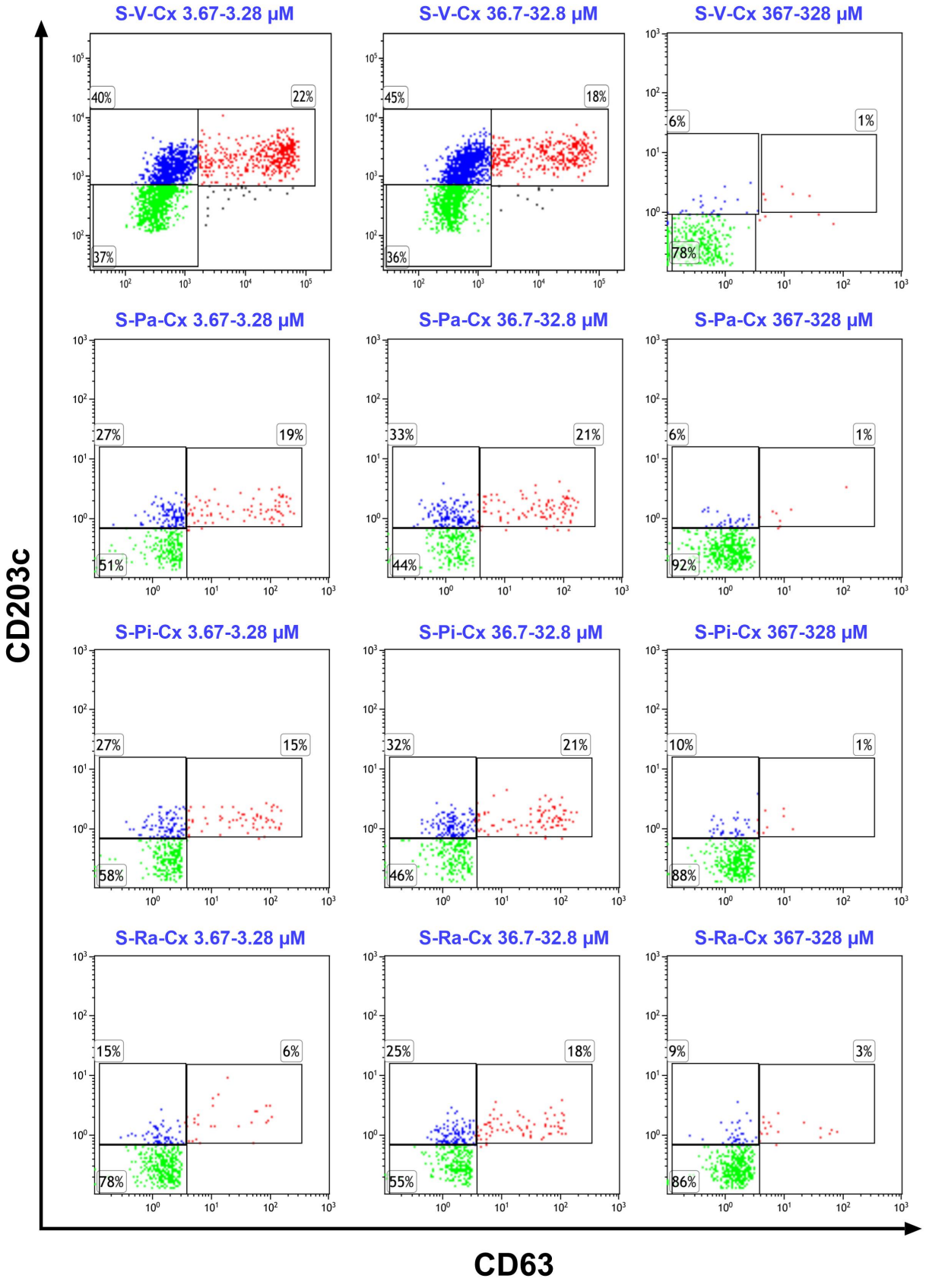
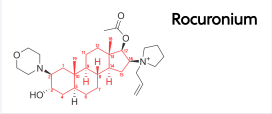
Table E1: substitutions at positions 2, 3, 16 and 17 for steroidal neuromuscular blocking agents (NMBAs)				
	Position 2	Position 3	Position 16	Position 17
rocuronium	Morpholino	hydroxy	allyl-pyrrolidinium	β-acetoxy
vecuronium	Piperidino	α-acetoxy	N-methyl-piperidino	β-acetoxy
Pipecuronium	4,4-dimethyl-piperazino	α-acetoxy	4,4-dimethyl-piperazino	β-acetoxy
pancuronium	N-methyl-piperidino	α-acetoxy	N-methyl-piperidino	β-acetoxy

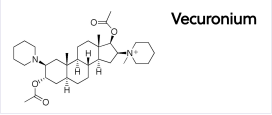

(a)
(b)
(c)
(d)

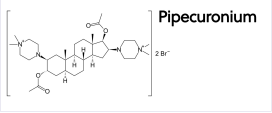

Selection basophils
Buffer
SSC (x 10³)
IgE+
IgE
CD203c
IgE+CD203c+
IgE
CD203c
3%
0%
95%
CD63
Rocuronium 3.28 µM
Rocuronium 32.8 µM
Rocuronium 328 µM
1%
0%
99%
2%
0%
96%
1%
0%
99%
Sugammadex 3.67 µM
Sugammadex 36.7 µM
Sugammadex 367 µM
CD203c
1%
0%
99%
2%
0%
96%
1%
0%
99%
S-R-Cx 3.67-3.28 µM
S-R-Cx 36.7-32.8 µM
S-R-Cx 367-328 µM
48%
14%
36%
28%
27%
40%
8%
1%
91%
CD63

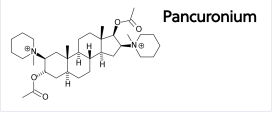

A
aIgE (5 μg/mL)
B
a
27%
70%
2%
b
61%
2%
36%
fMLP (0.25 μg/mL)
c
24%
47%
25%
d
24%
35%
36%
S-R-Cx (36.7-32.8 μM)
e
53%
25%
23%
f
32%
2%
66%
CD203c
CD63

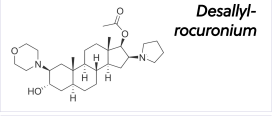

S-V-Cx 3.67-3.28 μM
40%
22%
37%
S-V-Cx 36.7-32.8 μM
45%
18%
36%
S-V-Cx 367-328 μM
6%
1%
78%
S-Pa-Cx 3.67-3.28 μM
27%
19%
51%
S-Pa-Cx 36.7-32.8 μM
33%
21%
44%
S-Pa-Cx 367-328 μM
6%
1%
92%
S-Pi-Cx 3.67-3.28 μM
27%
15%
58%
S-Pi-Cx 36.7-32.8 μM
32%
21%
46%
S-Pi-Cx 367-328 μM
10%
1%
88%
S-Ra-Cx 3.67-3.28 μM
15%
6%
78%
S-Ra-Cx 36.7-32.8 μM
25%
18%
55%
S-Ra-Cx 367-328 μM
9%
3%
86%
CD203c
CD63

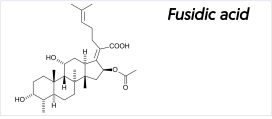












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With respect to confirmatory in vitro and skin tests see [3] for sIgE NMBA, [4] for skin testing and [5-7] for basophil activation tests (BAT). Mast cell activation was defined as acute tryptase exceeding 1.2xbaseline + 2 μg/L [8].

References of the repository

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