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Revisiting the role of MRGPRX2 on hypersensitivity reactions to neuromuscular blocking drugs

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Abstract

Anaphylaxis is caused by a variety of triggers including Food and Drug Administration (FDA)-approved antibiotics, contrast media and neuromuscular blocking drugs (NMBDs). Traditionally, drug-induced anaphylaxis was thought to result mainly from IgE-mediated histamine release from mast cells. Recently, a G protein-coupled receptor known as MRGPRX2 has been identified and shown to be highly expressed on human skin but not lung mast cells. The demonstration that many NMBDs induce degranulation in human mast cells via MRGPRX2 led to the idea that this receptor contributes to NMBD-induced hypersensitivity reactions. However, other studies have raised doubts regarding its role in drug-induced hypersensitivity. This review discusses the current status and controversy on MRGPRX2's role on NMBD-induced hypersensitivity.

Introduction

Anaphylaxis is an acute systemic hypersensitivity reaction that is evoked by a number of triggers including food, drugs and stinging insects. The definition of anaphylaxis is not uniform [1], but according to The American Academy of Allergy Asthma and Immunology it is a serious allergic response that often involves swelling, hives, lowered blood pressure and in severe cases, shock. If anaphylactic shock is not treated immediately, it can be fatal. Anaphylaxis to Food and Drug Administration (FDA)-approved antibiotics, opioids, contrast media and neuromuscular blocking drugs (NMBDs) have increased in recent years [2]. Many of these agents contain quaternary amino groups, which are considered as the main antigenic epitope [3]. NMBDs such mivacurium, atracurium, cisatracurium and rocuronium are used routinely in surgery to reduce unwanted muscle movement and to allow intratracheal intubation for mechanical ventilation but are responsible for about 60% of allergic reactions in surgical settings [4]. Based on classical concepts, most individuals that develop anaphylaxis to these drugs generate IgE antibodies, which bind to their cell surface high affinity receptors (FcεRI) mainly on mast cells (MCs, and basophils). Subsequent administration of the drug results in cross-linking of FcεRI-bound IgE leading to massive histamine release, which is responsible for the manifestations of anaphylaxis (Figure 1) [5,6••,7••].

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Nothing declared.

The clinical diagnosis of anaphylaxis to NMBDs is based on the presence of drug-specific IgE and biological signs of IgE-dependent cell activation (elevated tryptase, positive skin test, and positive basophil activation test, BAT; which is based on the upregulation of cell surface CD63 and CD203c following *ex vivo* incubation with the suspected drug) [7••,8,9]. Up to 15% of patients who encounter drug-induced reactions are allergic in nature but many do not exhibit biological signs of IgE-dependent immune cell activation [10,11], indicating the involvement of other potential mechanisms. IgG-mediated release of platelet-activating factor (PAF) from macrophages and basophils are thought to be involved in certain forms of anaphylaxis [12-14]. Jonsson *et al.* [6••], recently showed that concentrations of anti-NMBD IgG, neutrophil activation and PAF release correlate with anaphylaxis severity [6••]. Neutrophil activation is also observed in patients lacking evidence of classical IgE-dependent anaphylaxis [6••]. Thus, drug-induced anaphylaxis could reflect collective immune response involving IgE-mediated MC degranulation and IgG-mediated PAF release from basophils, macrophages and neutrophils (Figure 1).

NMBDs can also induce anaphylaxis in patients without previous exposure to the drugs [15]. Thus, drug-induced anaphylaxis can occur in drug-naïve patients either by immune-cross sensitization or via a non-immune mechanism [7••]. Immune-independent reactions or pseudoallergy can occur following intravenous injection of drugs at high doses leading to symptoms such as angioedema, urticaria, bronchospasm, gastrointestinal problems and hypotension [16]. These reactions are known as anaphylactoid reactions when the symptoms are severe. A novel G protein-coupled receptor (GPCR) known as Mas-related GPCR-X2 (MRGPRX2) has recently been shown to be expressed at high levels in skin human MCs, but low levels in lung and gut MCs [17••,18-20]. It is not found in normal macrophages and neutrophils but its status in basophils and eosinophils is the subject of controversy [17••,21,22••,23,24•,25]. McNeil *et al.* [10] found that of the 22 murine Mrg coding genes, mouse peritoneal MCs (PMCs) and skin MCs express MrgprB2, which has been designated as the mouse ortholog of human MRGPRX2, despite the fact that there is only ~53% overall sequence similarity between the two receptors [26]. NMBDs and other cationic drugs activate murine MCs both *in vitro* and *in vivo* via MrgprB2 [10,27,28]. Based on these findings, it was proposed that activation of MRGPRX2 contributes to drug-induced pseudoallergy in humans (Figure 1).

Since the original identification of MrgprB2 as the mouse counterpart of human MRGPRX2, there has been an explosion in research related to its involvement in pseudoallergy and inflammatory diseases. Most of these studies have been performed with a human MC line (LAD2 cells) that endogenously express MRGPRX2, mouse PMCs and MrgprB2$^{-/-}$ mice. In addition, a number of studies with human subjects have supported the idea that MRGPRX2 contributes to NMBD-induced hypersensitivity [29,30•,31-34], whereas others have questioned its role [7••,35]. Most of these controversies resulted from studies with rocuronium. This article will first describe the available evidence for MRGPRX2's role in mivacurium, atracurium and cisatracurium-induced hypersensitivity and then conclude with a discussion of the controversy related to rocuronium.

Mivacurium

Mivacurium is a short acting muscle relaxant that is widely used for surgical procedures particularly in infants and children with no increase in plasma histamine level [36]. However, intradermal administration of mivacurium leads to dose-dependent histamine release, causing vasodilatation, itch and pain [37,38]. Mivacurium induces degranulation in mouse PMCs and human LAD2 cells via MrgprB2 and MRGPRX2, respectively [10,28]. Che *et al.* [28] showed that mivacurium-induced paw edema and hypothermia are substantially reduced in MrgprB2$^{-/-}$ mice when compared to wild-type (WT) mice [28]. Based on these findings it was proposed that mivacurium causes pseudo-allergic reactions in humans via MRGPRX2 [28]. However, mivacurium can be injected in humans safely at a concentration of 2 mg/mL, which is higher than the concentration required to activate MRGPRX2 and MrgprB2 [10,28]. The reason for this difference is not clear but unlike many other MRGPRX2 agonists, mivacurium does not induce chemokine production in LAD2 cells [28]. It was proposed that the lack of cytokine generation by mivacurium in MCs reflects its relative safety profile in humans [28]. However, given that anaphylaxis is an acute reaction mostly mediated via the release of histamine and PAF from immune cells [5,6••], it is unclear how the lack of cytokine generation is associated with the safety profile of this drug. It is noteworthy that while all MCs are characterized via the expression of FcεRI, only cutaneous MCs express MRGPRX2 at high levels [17••,18,19]. It is therefore possible that local skin reaction induced by mivacurium reflects the activation of MRGPRX2 in cutaneous MCs without involving pseudo-allergic reactions [37,38]. Thus, caution should be exercised in translating the ability of mivacurium to cause paw edema and hypothermia in mice *in vivo* through MrgprB2 to pseudo-allergic reactions in humans via MRGPRX2 [28].

Atracurium and cisatracurium

Intradermal injection of atracurium in healthy volunteers results in wheal and flare responses, which are associated with degranulation of human skin MCs via an unknown mechanism [39,40]. It was later shown that atracurium activates human MCs via MRGPRX2 [10,34]. Additionally, injection of atracurium in WT mice leads to paw edema formation, which is substantially reduced in MrgprB2$^{-/-}$ mice [27]. Cisatracurium, a stereoisomer of atracurium, induces less histamine release and displays fewer allergy-like reactions than other NMBDs [41,42]. However, in some patients, cisatracurium may be associated with severe anaphylactic reactions possibly via IgE-mediated MC activation [43,44]. Cisatracurium also induces degranulation in LAD2 cells via MRGPRX2 and murine MCs via MrgprB2 [27,34]. Similar to mivacurium, cisatracurium does not induce chemokine generation despite causing robust degranulation [27,28]. It has recently been shown that MRGPRX2 activation by atracurium causes increased skin reactivity in patients with chronic spontaneous urticaria [24•]. This suggests that local skin reaction induced by atracurium and cisatracurium reflect the activation of skin MCs via MRGPRX2. However, any systemic effects of cisatracurium likely reflect IgE and IgG-mediated immune cell activation (Figure 1) [5,6••,43-45].

Rocuronium

In general, rocuronium has higher allergenic potential when compared to other NMBDs [45,46]. Not surprisingly, the mechanism of rocuronium-induced hypersensitivity has been studied most extensively. McNeil *et al.* [10] showed that rocuronium induces Ca^{2+} mobilization in transfected HEK293 cells expressing MrgprB2 and MRGPRX2 with EC_{50} values of 22.2 μg/mL and 263 μg/mL, respectively. The authors showed that rocuronium induces degranulation in mouse PMCs via MrgprB2 but they did not examine its effect on human MCs [10]. Based on mouse studies, it was proposed that MRGPRX2 contributes to rocuronium-induced hypersensitivity. However, Navinés-Ferrer *et al.* [34] showed that while cisatracurium at a concentration of 50 μg/mL induces significant degranulation in LAD2 cells via MRGPRX2, rocuronium at a concentration of up to 2 mg/mL has no effect. Other investigators also failed to demonstrate the ability of rocuronium to induce degranulation in RBL-2H3 cells stably expressing MRGPRX2 or human $CD34^+$ cell-derived primary human MCs, despite the fact that it induces a robust response in mouse PMCs [29,30•,34,47].

The differences in the ability of rocuronium to activate MrgprB2 and MRGPRX2 is surprising and could reflect the fact that there is only ~53% sequence homology between the human and the mouse receptor [10]. Interestingly, compound 48/80, a polymer with a strong positive charge and multiple bulky hydrophobic moieties, is one of the most potent MRGPRX2 agonists known with a potency of ~130-fold higher than for MrgprB2 [10]. Although rocuronium has one quaternary amine and another amine that is mostly positively charged at pH 7.4, its hydrophobic steroidal backbone lacks the aromatic ring present in higher affinity MRGPRX2 agonists such as ZINC3573 and compound 48/80 [10,48,49]. Thus, in addition to positive charges, the hydrophobic moieties may be required for agonist binding to MRGPRX2 but it may interfere agonist-MrgprB2 interaction.

Given that rocuronium induces Ca^{2+} mobilization in HEK293 cells expressing MRGPRX2 and $CD34^+$ cell-derived primary human MCs [10,47], it was surprising that it did not induce degranulation via MRGPRX2 [29,30•,47]. To resolve this discrepancy, Chompunud Na Ayudhya *et al.* [50••] conducted a comprehensive study using mouse PMCs, RBL-2H3 cells stably expressing MRGPRX2, LAD2 cells and human skin MCs. The authors found that, consistent with the previously reported EC_{50} value for Ca^{2+} mobilization in MrgprB2 transfected HEK293 cells [10], rocuronium at 20 μg/mL caused significant degranulation in mouse PMCs and that this response was abolished in PMCs derived from $MrgprB2^{-/-}$ mice. However, unlike previous reports, rocuronium was found to induce degranulation in transfected RBL-2H3 cells and LAD2 cells with an EC_{50} value of ~500 μg/mL and reaching maximal response at 2 mg/mL. Rocuronium also induced degranulation in human skin MCs but the magnitude of the response was much lower than that in LAD2 or transfected RBL-2H3 cells, which reflected lower level of MRGPRX2 expression. Thus, these findings provided the first demonstration that rocuronium induces degranulation in human MCs via MRGPRX2. Furthermore, the important difference between mouse MrgprB2 and human MRGPRX2 demonstrate the difficulty in translating findings from mice to humans.

Spoerl *et al.* [32] reported three cases of rocuronium-induced hypersensitivity; these patients had no increase in serum IgE and displayed a negative BAT. The authors found that

undiluted rocuronium (10 mg/mL) induces small and variable skin reaction. This effect likely reflects the direct activation of MRGPRX2 in cutaneous MCs by rocuronium [50••]. Sugammadex is a γ-cyclodextrin that encapsulates NMBDs such as rocuronium, preventing its interaction with the nicotinic receptor, and thereby reversing neuromuscular blockade [32,51]. Sugammadex inhibits both rocuronium-induced MRGPRX2-mediated signaling in MCs *in vitro* and irritative skin reactions *in vivo* [29,32]. Based on these findings, it was proposed that MRGPRX2 plays an important role in drug-induced pseudoallergy and that this reaction should be re-classified as type A adverse reaction [32,33].

Consistent with findings discussed above, Suzuki *et al.* [30•] reported a case of hypersensitivity reaction to rocuronium; intradermal skin testing with undiluted rocuronium (10 mg/mL) resulted in a positive reaction but total IgE and specific IgE to rocuronium were negative. Based on these findings, this patient was diagnosed with non-IgE-mediated allergic reaction. Moreover, sequence analysis of genomic DNA of this patient revealed three amino acid mutations (M196I, L226P and L237P) in MRGPRX2 [30•]. These mutations are located in MRGPRX2's 5th and 6th transmembrane (TM) domains in close proximity to its ligand binding pocket (Figure 2) [48,52,53]. The authors suggested that these mutations would enhance the affinity of MRGPRX2 for rocuronium, thus providing genetic evidence for the role of MRGPRX2 on rocuronium-induced hypersensitivity [30•]. Lansu *et al.* [48] identified an MRGPRX2 mutation in its ligand binding pocket (E164D) that increases the receptor affinity for certain drugs. Sequence alignment predicts that MrgprB2's E171 is likely the residue that 'sits' in the MRGPRX2 E164 position [52]. Thus, it is quite possible that MRGPRX2 mutations found in a patient with rocuronium hypersensitivity [30•] may allosterically modify the receptor for ligand binding/signalling so that the receptor functions similar to mouse MrgprB2 for enhanced responsiveness to rocuronium and other NMBDs.

Chompunud Na Ayudhya *et al.* [50••] constructed cDNAs encoding MRGPRX2 variants M196I, L226P and L237P and generated separate transient transfectants expressing each variant in RBL-2H3 cells. They found that while M196I and L226P variants were expressed on the cell surface at a level similar to WT MRGPRX2, L237P variant displayed reduced expression (Figure 2). Surprisingly, cells expressing L226P and L237P variants showed loss-of-function phenotype for MC degranulation in response to rocuronium, while cells expressing M196I variant responded similarly to the WT receptor. Cells expressing double (M196I, L226P) or triple variants (M196I, L226P and L237P) were also hypo-responsive to rocuronium (1 mg/mL) for degranulation (Figure 2) [50••]. These findings suggest that the weak erythema response to intradermal injection of 10 mg/mL rocuronium results from low level of degranulation through the activation of the mutated MRGPRX2 and does not support its role in hypersensitivity reaction observed in this patient [30•,50••]. In addition to rocuronium, this patient was also exposed to remifentanil, latex and chlorhexidine, and the possibility that the hypersensitivity reaction in this patient could have resulted from one or more of these agents was not considered [30•]. Furthermore, a negative rocuronium-specific IgE result does not rule out an IgE-mediated rocuronium allergy [30•,54]. Thus, it is possible that hypersensitivity reaction to rocuronium reported by Suzuki *et al.* [30•] may be unrelated to MRGPRX2 activation.

The most convincing evidence that rocuronium does not contribute to rocuronium hypersensitivity in most patients came from Van Gasse *et al.* [7••] who conducted a study with 140 patients suspected of hypersensitivity to rocuronium. The authors utilized a diagnostic approach that included measurement of serum tryptase level, quantification of specific IgE antibodies to rocuronium, intradermal skin test (50 μg/mL rocuronium) and BAT. Using this approach it was concluded that rocuronium-induced hypersensitivity in most patients resulted from IgE-mediated MC activation.

Conclusions

The seminal observation by McNeil *et al.* [10] that NMBDs induce degranulation in mouse PMCs via MrgprB2 led to the notion that these drugs induce hypersensitivity reactions in humans via MRGPRX2. Although a number of studies with human subjects supported this conclusion, others have not [7••,29,30•,31-34]. In this context, it is noteworthy that of the NMBDs tested, rocuronium has the least potency for inducing degranulation in human MCs via MRGPRX2 but has the highest allergenic potential [7••,45,46]. It now appears that the mechanism of rocuronium-induced hypersensitivity in most patients involves IgE-mediated MC-degranulation and possibly IgG-mediated PAF release from basophils, macrophages and neutrophils (Figure 1) [5,6••,7••,35]. In addition, MRGPRX2 mutations in a patient with rocuronium hypersensitivity are not associated with gain-of-function phenotype for MC degranulation *in vitro* [30•,50••].

Peptidergic drugs such as icatibant, cetrorelix, leuprolide, octreolide and sermorelin that induce injection site swelling, pain or pruritus in humans activate murine PMCs via MrgprB2 [10] but none of these drugs are associated with anaphylaxis. Given that MRGPRX2 is expressed predominantly in human skin MCs, this raises the interesting possibility that injection site reaction such as erythema and swelling observed following intradermal administration of high concentration of rocuronium (up to 10 mg/mL) [30•,32] likely reflects skin MC degranulation via MRGPRX2 [50••].

While MRGPRX2 is expressed predominantly in skin MCs, it is found at low levels in lung and gut MCs and whether or not it is expressed in normal basophils is the subject of current controversy [21,22••,23,24•,25]. It is therefore possible that gain-of-function mutations in MRGPRX2 or its increased expression in skin, lung and gut MCs and basophils could lead to pseudoallergy or anaphylactoid reaction in certain individuals. It is important to note that anaphylaxis is a highly complex disease with intrinsic factors such as higher age, male sex, concomitant mastocytosis and extrinsic factors including vigorous exercise, psychological burden and drugs (β-blockers and angiotensin-converting enzyme inhibitors) may modulate the severity of the disease [55-57]. In addition, there is a tremendous variability in the individual responsiveness of cutaneous MCs to MRGPRX2 agonists [58,59]. Therefore, further studies will be required to more precisely delineate the roles of MRGPRX2 on the activation and modulation of drug-induced hypersensitivity reactions.

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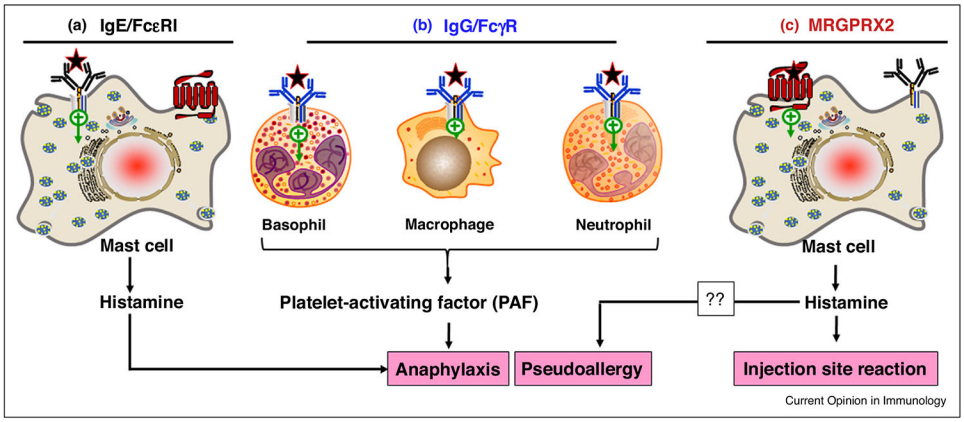
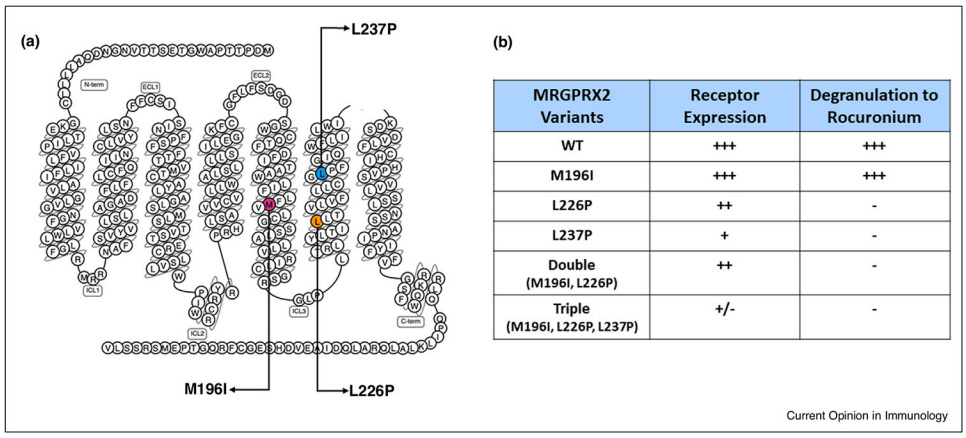


Figure 1.

Potential mechanism for NMBD–mediated anaphylaxis. **(a)** Most individuals that develop anaphylaxis to NMBDs generate IgE antibodies, which bind to their cell surface high affinity receptors (FcεRI) mainly on mast cells (also basophils not shown). Subsequent administration of the drug results in the cross-linking of FcεRI-bound IgE leading to massive histamine release, which is responsible for the manifestations of anaphylaxis. **(b)** IgG antibodies are also be generated in response to certain NMBDs. These antibodies bind to FcγRI on the surface of basophils, macrophages and neutrophils. Subsequent exposure to the drug leads to immune complex formation and activation of FcγRI, resulting in the generation of PAF. This pathway could aggravate IgE-mediated anaphylaxis or could form the underlying mechanism of anaphylaxis in the absence of IgE [6••]. **(c)** It has been proposed that activation of cutaneous MCs by NMBDs via MRGPRX2 and the subsequent mediator release leads to pseudoallergy. Whether or not this pathway plays an important role in NMBD-induced anaphylaxis remains to be confirmed. NMBDs that activate cutaneous MCs via MRGPRX2 likely cause local erythema and swelling (injection site reaction) due to histamine release.



MRGPRX2 Variants	Receptor Expression	Degranulation to Rocuronium
WT	+++	+++
M196I	+++	+++
L226P	++	-
L237P	+	-
Double (M196I, L226P)	++	-
Triple (M196I, L226P, L237P)	+/-	-

Figure 2.

Missense MRGPRX2 variants and their responsiveness to rocuronium. **(a)** Snake diagram of MRGPRX2 indicating three missense mutations identified in a patient diagnosed with non-IgE-mediated rocuronium hypersensitivity [30•]. **(b)** Data summarizing expression of wild-type (WT), single, double and triple variants of MRGPRX2 in transiently transfected RBL-2H3 cells and their responsiveness to rocuronium for degranulation [50••].