

An alternative explanation for immediate hypersensitivity reactions to opioids



To the Editor:

We read the publication on opioid hypersensitivity by Li et al¹ with great interest. It clearly highlights the difficulties and uncertainties associated with a correct diagnosis of genuine IgE/FcεRI opioid allergy. The authors finally state that, for the time being, there is no *in vitro* nor *in vivo* test that enables us to differentiate between usually clinically indistinguishable IgE/FcεRI-dependent and non-IgE/FcεRI-dependent reactions with absolute certainty. However, we would like to draw attention to the Mas-related G protein coupled receptor X2 (MRGPRX2) as an alternative explanation of their findings and challenge their statement regarding the value of *in vitro* tests in “opioid allergy.” The Mas-related G protein-coupled receptors (Mrgprs) comprise a subfamily of receptors named after the first discovered member, Mas. At present, more than 50 Mrgprs have been identified and are now divided into several subfamilies being renamed to a novel nomenclature (<http://www.guidetopharmacology.org>) including the primate-specific MRGPRX subfamily. Human MRGPRX are expressed by various cell types including dorsal root ganglion neurons and connective tissue mast cells (MC_{TC}), the latter mainly expressing the MRGPRX2 that is activated by various basic small molecules, such as the neuropeptide substance P, antimicrobial host defense proteins, anaphylatoxins C3a and C5a, and compound 48/80, leading to degranulation independent from cross-linking of IgE/FcεRI complexes.²

Recently, McNeil et al³ demonstrated that the MRGPRX2 might also be involved in mast cell-driven immediate drug hypersensitivity reactions (IDHR) toward compounds such as the bradykinin receptor 2 antagonist icatibant, curarizing neuromuscular blocking agents (atracurium, rocuronium), and several fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin). Recently similar observations were made for many opioid compounds (including morphine, codeine and different major metabolites).⁴ The quintessence of these studies is clear, namely off-target occupancy of the MRGPRX2 receptor is increasingly recognized as a novel nonimmune endotype of mast cell-driven IDHR. Moreover, the cellular distribution of the MRGPRX2 might explain some clinical and biological peculiarities of the opioid hypersensitivity scene. Actually, the observation that the MRGPRX2 is mainly expressed on skin mast cells might explain the almost invariant presence of cutaneous symptoms in both index and challenge reactions as described by Li et al,¹ as well as the uncertainties associated with skin testing for opiates. Alternatively, as basophils barely express the MRGPRX2,⁵ and as described in this journal,⁶ because these cells do not respond nonspecifically on opiates in control individuals uneventfully challenged with morphine and/or codeine, it seems justified to speculate that basophil activation experiments might constitute a reliable diagnostic to document genuine IgE/FcεRI-mediated opiate hypersensitivity and related cross-reactivities.⁷ Moreover, it is likely that conditioned basophils, namely basophils expressing the MRGPRX2,⁵ might allow entrance of a readily accessible human model to further explore the ability of opioids to activate the MRGPRX2 receptor.

In essence, we appreciated the study by Li et al.¹ However, we felt it was appropriate to draw attention to (a) off-target activation

of the MRGPRX2 receptor as an alternative explanation for their observations, and (b) the potential of basophil activation experiments in distinguishing between IgE/FcεRI-mediated and MRGPRX2-mediated opioid hypersensitivity.

Acknowledgments

ALVG is a fellow of the Fonds voor Wetenschappelijk Onderzoek - Vlaanderen (FWO) (1113617N). VS is a senior clinical researcher of the FWO (1804518N). DGE is a senior clinical researcher of the FWO (1800614N).

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No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication August 1, 2017; accepted for publication August 2, 2017.

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<http://dx.doi.org/10.1016/j.jaip.2017.08.016>

Reply



To the Editor:

We thank Van Gasse et al¹ for their interest in our paper² and discussing the role of Mas-related G protein-coupled receptors in the pathomechanism of opioid allergy. Their activation might indeed explain certain aspects of opioid hypersensitivity reactions.

Our pragmatic, “real-life” study focused on the clinical predictors of opioid hypersensitivity and the importance of drug provocation testing (DPT). We fully appreciate the need for safe, precise, and less time-consuming testing methods than DPT. However, despite tremendous progress in the recent years, there

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