The bronchodilatory capacity of imiquimod: the existence of two mechanisms

Olivia J. Larsson,1 Martijn L. Manson,3,4 Magnus Starkhammar,1,3 Barbara Fuchs,1 Mikael Adner,3,4 Susanna Kumlien Georén,1,3 and Lars-Olaf Cardell1,2

1Division of ENT Diseases, CLINTEC, Karolinska Institutet, Stockholm, Sweden; 2Department of ENT Disease, Karolinska University Hospital, Stockholm, Sweden; 3Centre for Allergy Research, Karolinska Institutet, Stockholm, Sweden; and
4Institute for Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

TO THE EDITOR: We recently published a study investigating the bronchodilatory capacity of the Toll-like receptor 7 (TLR7) agonist imiquimod, establishing the presence of a nonneuronal, TLR7-independent mechanism of dilation (9). Our study adds new information to the previously published reports, which demonstrated that relaxation can be mediated by a TLR7-independent release of nitric oxide (NO) from innervating nerves (2, 5). In a Letter to the Editor, Drake (2a) now argues that the data we report do not provide sufficient evidence to support our conclusion of a nonneuronal TLR7-independent mechanism. We would instead argue that our results are sound and reflect the presence of an additional mechanism for imiquimod-mediated bronchodilation.

In our study, we demonstrated that administration of the neurotoxin tetrodotoxin (TTX) in vitro had no effect on imiquimod-induced bronchodilation and thus concluded that neuronal pathways were not involved in dilation (9). Due to the presence of TTX-resistant nerves, particularly those originating from the nodose ganglia (8), Drake suggests that this is not sufficient to discount neuronal involvement. However, the contribution of TTX-resistant nodose-derived sensory nerves to relaxation is unlikely. Although these nerves contain relaxatory mediators, namely pituitary adenylate cyclase-activating polypeptide (PACAP) (1, 3) and substance P (SP) (4, 12), SP induces relaxation via the epithelium (4) and PACAP relaxes independently of nitric oxide synthase (NOS) (7). This argues against Drake’s proposed mechanism of epithelium-independent and NO-mediated relaxation. In addition, activation of sensory neurons by imiquimod has been shown to be TLR7 independent (6), which suggests that a TLR7-dependent neuronal mechanism of relaxation does not occur via sensory neurons. We could further demonstrate in our study that all nerve-mediated relaxation was blocked by TTX (9). NO-releasing inhibitory nonadrenergic, noncholinergic (iNANC) fibers have repeatedly been shown to be TTX sensitive (10), suggesting that our use of TTX was sufficient to evaluate and discount the possible contribution of NO-mediated neuronal relaxation, the mechanism proposed by Drake and colleagues.

Noticeably, there are discrepancies between our results and those published previously by Drake and colleagues, particularly from experiments assessing the roles of TLR7 and NO, those published previously by Drake and colleagues, particularly from experiments assessing the roles of TLR7 and NO, which can affect the extent of neuronal innervation. Indeed, the fact that we identified a small role for NO in vivo, as highlighted by Drake, could suggest that the relative presence or absence of intact nerves is of importance in identifying a neuronal TLR7-dependent mechanism for dilation.

We would like to reiterate our study does not dispute that of Drake and colleagues but purely supplies an additional mechanism for imiquimod-mediated bronchodilation. Using a nerve-free setup with isolated airway smooth muscle, we identified that imiquimod could additionally directly influence histamine-induced Ca2+ flux in smooth muscle cells in a TLR7-independent manner. In addition, as shown previously by Drake and colleagues (5), inhibition of NO or TLR7 does not fully reverse the dilatory effects of imiquimod, suggesting that another mechanism feasibly exists. The relative contribution of respective mechanisms may be dependent on the model used, the route of administration of imiquimod, and the relative presence of neuronal innervation. The complexity of imiquimod-mediated bronchodilation is fascinating and is likely to be of use in the development of novel fast-acting, bronchodilatory compounds.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

REFERENCES

Address for reprint requests and other correspondence: L. O. Cardell, Division of ENT Diseases, CLINTEC, Karolinska Institutet, SE-141 57, Stockholm, Sweden (e-mail: lars-olaf.cardell@ki.se).

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