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Implications of MRGPRX2 in human and experimental cardiometabolic diseases

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We read the excellent Review by Guo-Ping Shi *et al.* (Mast cells in human and experimental cardiometabolic diseases. *Nat. Rev. Cardiol.* **12**, 643–658; 2015)[1] with great interest. The authors proposed a role for neuropeptides in the activation of cardiac and coronary mast cells, with a specific focus on the role of substance P in these processes. The authors suggest an association between cardiovascular events and allergies. We are interested in basic mechanisms mediating itch. Indeed, a role for substance P and neuropeptides and their interaction with mast cells in the context of itch, allergy, and inflammatory skin disease is parallel to cardiometabolic events. On the basis of previous studies[2], the authors conclude that substance P activates mast cells via its cognate receptor, neurokinin 1 (NK-1R; also known as tachykinin receptor 1), to induce mast cell degranulation and subsequent inflammation. We respectfully disagree with involvement of NK-1R in substance P-induced mast cell degranulation. A plethora of studies have demonstrated that substance P-induced mast cell degranulation and inflammatory properties are mediated via a member of the Mas-related G-protein coupled receptors (MRGPRs), MRGPRX2 (REFS 3–5). The mouse orthologue of MRGPRX2 is Mrgprb2 (REF. 3). Substance P-induced mast cell degranulation is diminished in mast cells from *Mrgprb2*$^{-/-}$ mice[3]. We have identified that antagonists of NK-1R have an off-target inhibitory effect on mouse Mrgprb2, but not human MRGPRX2 (REF. 4). This finding is critical, because almost all studies in the field of cardiometabolic disease, including the ones cited by Guo-Ping *et al.*, have used NK-1R antagonists and not *Nk1r*$^{-/-}$ (*Tacr1*$^{-/-}$) mice to demonstrate that substance P activation of cardiac and coronary mast cells is NK-1R-dependent.

NK-1R antagonists have long been investigated for treating inflammatory conditions associated with mast cells, such as migraine and asthma. Despite promising preclinical results in animal models, NK-1R antagonists were ineffective in clinical trials of inflammatory diseases[6,7]. Given that substance P-induced mast cell degranulation is mediated via MRGPRs, and NK-1R antagonists inhibit mouse Mrgprb2, but not human MRGPRX2, the inefficacy of NK-1R antagonists in treating mast-cell-associated inflammation is no longer a surprise.

Our Correspondence has several implications for future studies in the field of cardiology, for elucidating the role of neuropeptides and mast cells, and for identification of new drug targets in this field. First, the anti-inflammatory effects of NK-1R antagonists in animal models of cardiac disease are not predictive of their efficacy in humans. Second, MRGPRX2, a receptor implicated in itch[4,8] but, to our knowledge, not in any cardiac disease, is mediating substance P-induced mast cell degranulation and might be contributing to pathogenesis of various cardiometabolic disorders. Third, given the pivotal role of MRGPRX2 in itch[4,5,8], allergy[3], and inflammation[3,4], this receptor might be one of the links between cardiovascular events and allergies. Finally as Shi *et al.* concluded, we believe that novel mast cell stabilizers might have implications for treating various cardiometabolic diseases, and MRGPRX2 antagonists[4] are interesting novel candidates.

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Competing interests statement
The authors declare no competing interests.