Abstract: 23O

Bitter Taste Receptors (T2Rs) in the Heart – a New Cardiovascular Physiology?

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BACKGROUND: The human genome contains 25 bitter taste receptors (T2Rs), which are responsible for detecting thousands of bitter ligands, including toxic and aversive compounds. This sentinel function in the mouth varies significantly between individuals and is underpinned by natural genetic polymorphisms. Recent studies, from us and others, have reported the expression of T2Rs and their downstream signalling components within non-gustatory tissues, including the heart. The precise function of T2Rs and the implication of the polymorphic variants remains to elucidated. *METHODS:* To identify the role of T2Rs within the cardiovascular system, we generated a series of naturally occurring receptor variants and tested their functional capacity *in vitro;* we tested T2R ligands on explanted human heart tissue and tested their functional capacity *in vitro* and developed a novel humanised mouse model using a cardiomyocyte-specific virus (AAV9-cTnT-T2R46-eGFP). *RESULTS:* Naturally occurring single nucleotide polymorphisms (SNPs) rendered T2R14, -30 and -46 non-functional in calcium mobilisation signalling assays. Furthermore, the application of picrotoxinin (a T2R30 and T2R46 ligand) on explanted human heart tissue resulted in significant cardiodepression. Because this function did not associate with any of the specific T2R SNP genotypes, we next developed a humanised mouse cardiac model of T2R46, whereby an adeno-associated virus was used to selectively express the human T2R46 in mouse cardiomyocytes. Under basal conditions, this expression did not alter cardiac function (determined by echocardiography and langendorff preparations) relative to non-infected mice, but negative inotropic effects (decreased cardiac output and stroke volume) were observed in hearts expressing T2R46 upon intravenous injection of picrotoxinin. *CONCLUSIONS:* This study is the first to unequivocally demonstrate a cardio-depressive function for T2Rs in heart. It is anticipated that highly penetrant, cardiac-expressed T2R polymorphisms combined with novel humanised mouse models, generated using cardiac cell-specific AAVs, will prove critical in revealing the contribution of T2Rs to cardiac physiology.