Molecular determinants and functional consequences of the β_{1L}-adrenoceptor in the heart

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The β_1-adrenoceptor (β_1AR) is activated by (-)-noradrenaline and blocked by all clinically used β-blockers. Some β-blockers, typified by (-)-CGP 12177 and (-)-pindolol not only block the β_1AR, but also activate it at higher concentrations (~2-3 orders of magnitude) than those required to block it (Kaumann & Molenaar, 2008). To accommodate these findings, it was hypothesized that β-blockers such as (-)-CGP 12177 and (-)-pindolol bind to the β_1AR at two different sites, one that *blocks* (-)-noradrenaline from activating the receptor, the β_{1H} site, and another that *activates* the receptor, the β_{1L} site. Acute activation of β_{1L}ARs in the heart causes increases in contractile force, hastening of relaxation and increases the probability of arrhythmias (Kaumann & Molenaar, 2008). We have now sought to determine (1) the molecular determinants of the β_{1L}AR and (2) the functional and pathological consequences of chronic activation of β_{1L}AR. β_1ARs, β_2ARs and mutant β_1ARs containing all (β_1(β_2TMDV)AR) or single amino acids of the fifth transmembrane domain (TMDV) β_2AR were prepared and stably expressed in Chinese Hamster Ovary cells. Substitution of heterologous β_2AR isoluceine for valine230 in TMDV of the β_1AR reduced the ability of the β_1AR to form a low affinity binding site of the β_1AR. In mice, chronic infusion of (-)-CGP 12177 (0.01 mg 100 mg/kg/24h *via* osmotic minipump) for 2 or 4 weeks caused a dose-dependent increase in heart rate and cardiac contraction measured as fractional shortening (FS %) which was maintained for 4 weeks. In mice with trans-aortic constriction reducing lumen size by ~60-65% for a period of 8 weeks, chronic activation of β_{1L}AR with (-)-CGP 12177 during weeks 5-8 caused a more severe cardiac hypertrophy, interstitial fibrosis and inflammation compared to trans-aortic constriction alone, indicating more severe myocardial remodelling. We conclude that chronic activation of β_{1L}AR can be potentially harmful.

Kaumann AJ & Molenaar P (2008) *Pharmacology & Therapeutics* **118,** 303-336.