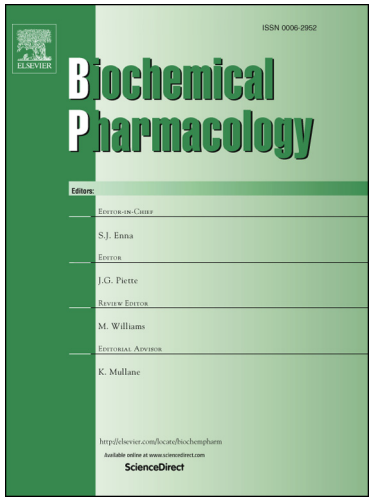

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Characterisation of signalling and regulation of common calcitonin receptor splice variants and polymorphisms

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Abstract:

The calcitonin receptor (CTR) is a class B G protein-coupled receptor that is a therapeutic target for the treatment of hypercalcaemia of malignancy, Paget's disease and osteoporosis. In primates, the CTR is subject to alternative splicing, with a unique, primate-specific splice variant being preferentially expressed in reproductive organs, lung and kidney. In addition, humans possess a common non-synonymous single-nucleotide polymorphism (SNP) encoding a proline/leucine substitution in the C-terminal tail. In low power studies, the leucine polymorphism has been associated with increased risk of osteoporosis in East Asian populations and, independently, with increased risk of kidney stone disease in a central Asian population. The CTR is pleiotropically coupled, though the relative physiological importance of these pathways is poorly understood. Using both COS-7 and HEK293 cells recombinantly expressing human CTR, we have characterized both splice variant and polymorphism dependent response to CTs from several species in key signalling pathways and competition binding assays. These data indicate that the naturally occurring changes to the intracellular face of CTR alter ligand affinity and signalling, in a pathway and agonist dependent manner. These results further support the potential for these primate-specific CTR variants to engender different physiological responses. In addition, we report that the CTR exhibits