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Analysis of cGKI inhibition by Rp-cGMP analogs

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Although it is well established that cGMP has important (patho-)physiological functions, the downstream mediators of cGMP signalling are not well understood. The cGMP-dependent protein kinase type I (cGKI) is an attractive candidate receptor for cGMP. A common approach to distinguish between cGKI-dependent and cGKI-independent cGMP effects is the use of pharmacological "cGKI inhibitors". However, it is increasingly recognized that some of these drugs, such as KT5823, may be less specific than previously thought or may not at all inhibit cGKI activity in intact cells. The Rp-cGMP analogs are reported to inhibit cGKI by binding to the cGMP-binding sites. In this study, we have analysed the effects of two popular Rp-cGMP analogs, Rp-8-Br-PET-cGMPS and Rp-8-pCPT-cGMPS, on basal and cGMP/cGKI-stimulated growth of vascular smooth muscle cells. Surprisingly, neither compound showed a clear inhibition of cell growth and cGKI activity in intact cells as monitored by growth assays and phosphorylation of vasodilator-stimulated phosphoprotein (VASP), respectively. In vitro kinase assays with purified cGKI demonstrated that both Rp-cGMP analogs are partial agonists for cGKI rather than antagonists (see Figure 1). Thus, it appears difficult to interpret data obtained from experiments with Rp-8-Br-PET-cGMPS and Rp-8-pCPT-cGMPS. Both compounds should be used with caution as "cGKI inhibitors".

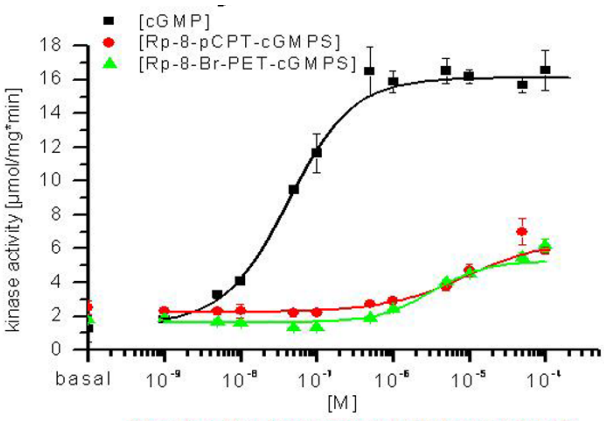

Figure 1
Effects of the Rp-cGMP isomers on basal cGKI activity *in vitro*.