Altered desensitization and internalization patterns of rodent versus human GIP receptors – a major drug discovery challenge

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Abstract

Background and Purpose The gut hormone glucose-dependent insulinotropic polypeptide (GIP) signals via the GIP receptor (GIPR) resulting in postprandial processes such as potentiation of glucose-stimulated insulin secretion. Translation of results from rodent to human studies has, however, been challenged by contradictive therapeutic effects of GIPR-targeting compounds. We, therefore, investigated the variation between species focusing on GIPR desensitization and the role of the C-terminus. Experimental Approach Species variants of the GIPR were studied *in vitro* for endogenous ligand affinity, G protein activation (cAMP accumulation), recruitment of beta-arrestin, and internalization. Variants of the mouse, rat, and human GIPRs with swapped C-terminal tails were studied in parallel. Key Results The human GIPR is more prone to internalization than rodent GIPRs. Despite similar agonist affinities and potencies for $G_{\alpha s}$-activation especially the mouse GIPR has a reduced receptor desensitization, internalization, and beta-arrestin recruitment. Using an enzyme-stable, long-acting GIP analogue, the species differences were even more pronounced. "Tail swapped" human, rat, and mouse GIPRs were all fully functional in their $G_{\alpha s}$-coupling and the mouse GIPR regained internalization and beta-arrestin 2-recruitment properties with the human tail while the human GIPR lost the ability to recruit beta-arrestin 2 when its own C-terminus was replaced by the rat or mouse tail. Conclusion and Implications Desensitization of the human GIPR is dependent on the C-terminal tail. The diverse functionality of the C-terminal tail as well as receptor internalization patterns between species, especially human and mouse GIPRs, are important factors that could influence the preclinical therapeutic evaluation of GIPR targeting compounds.

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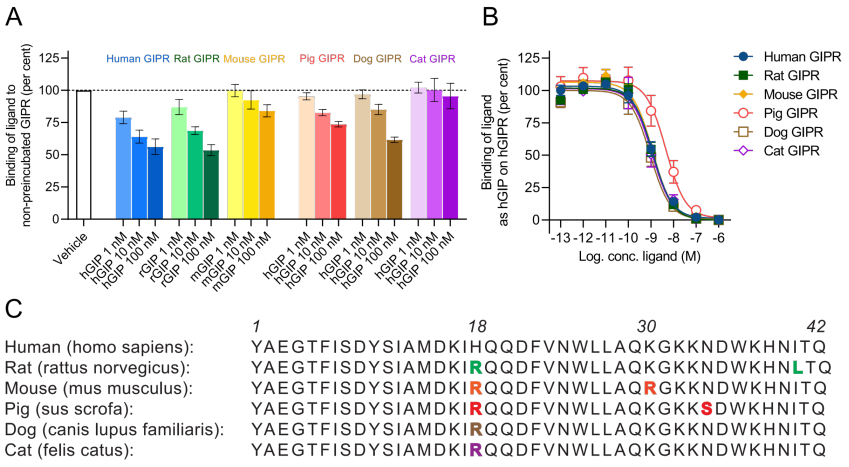

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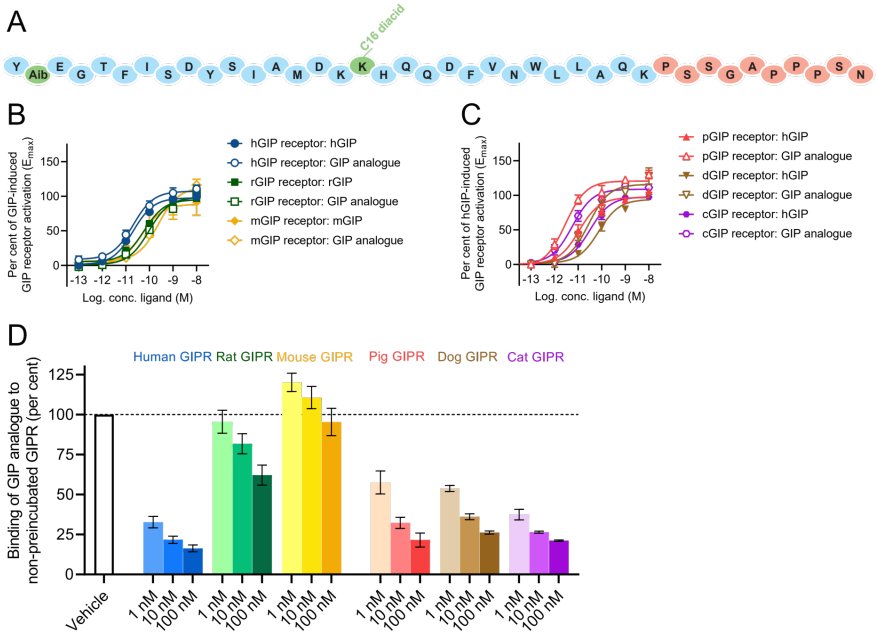
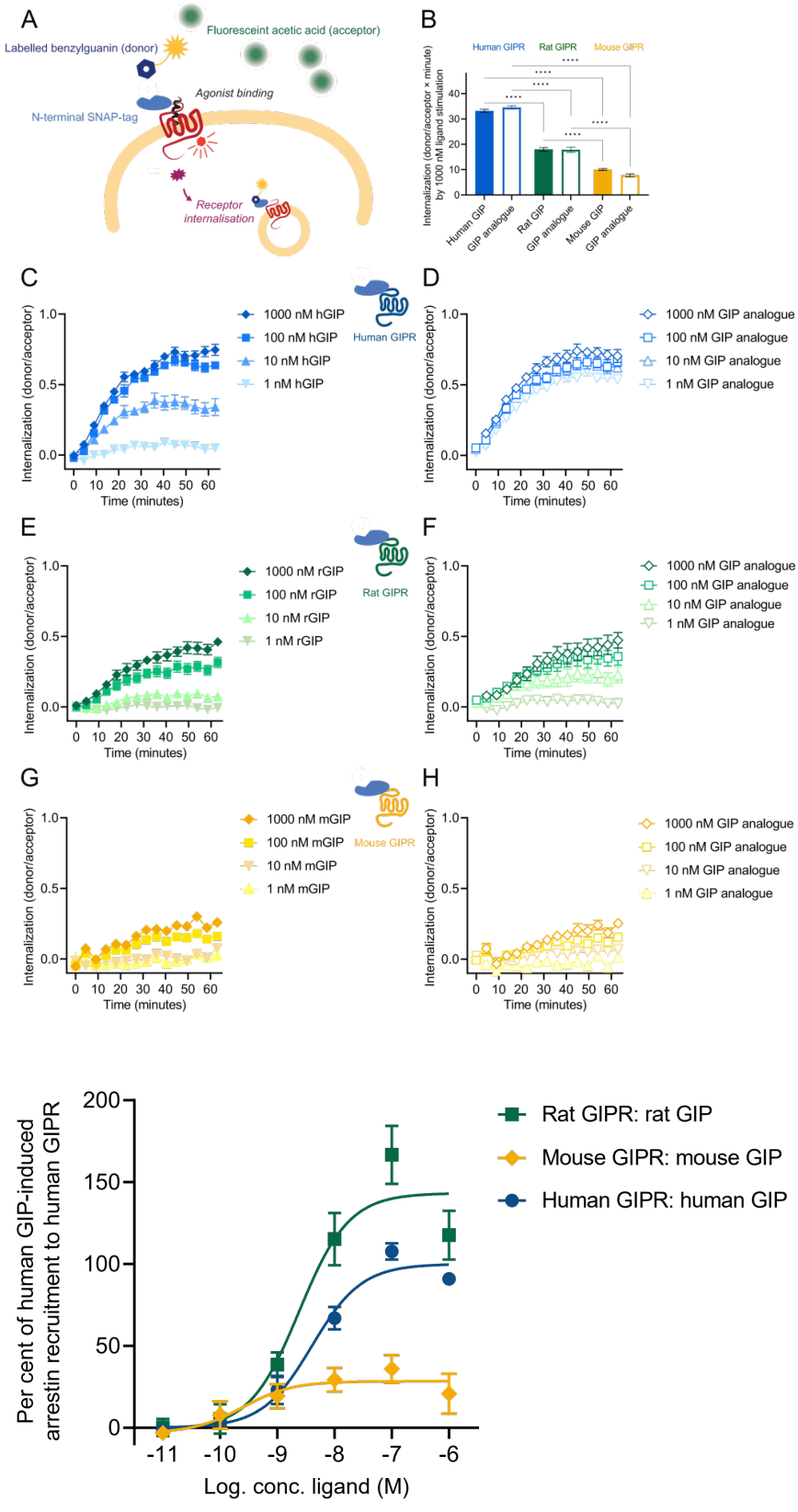
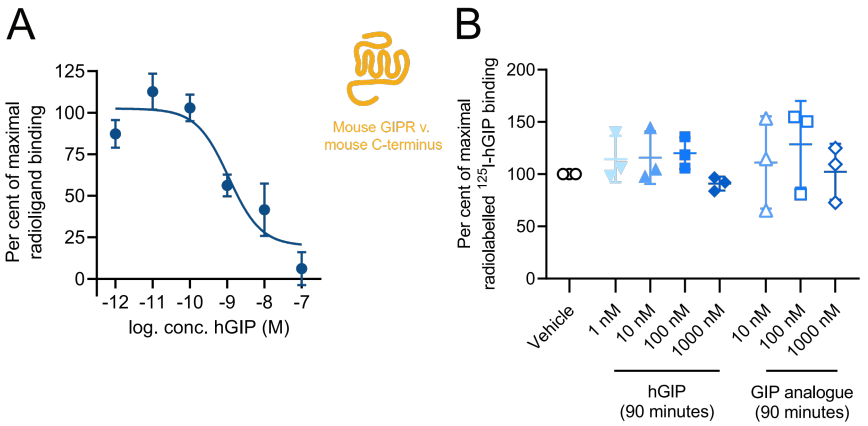
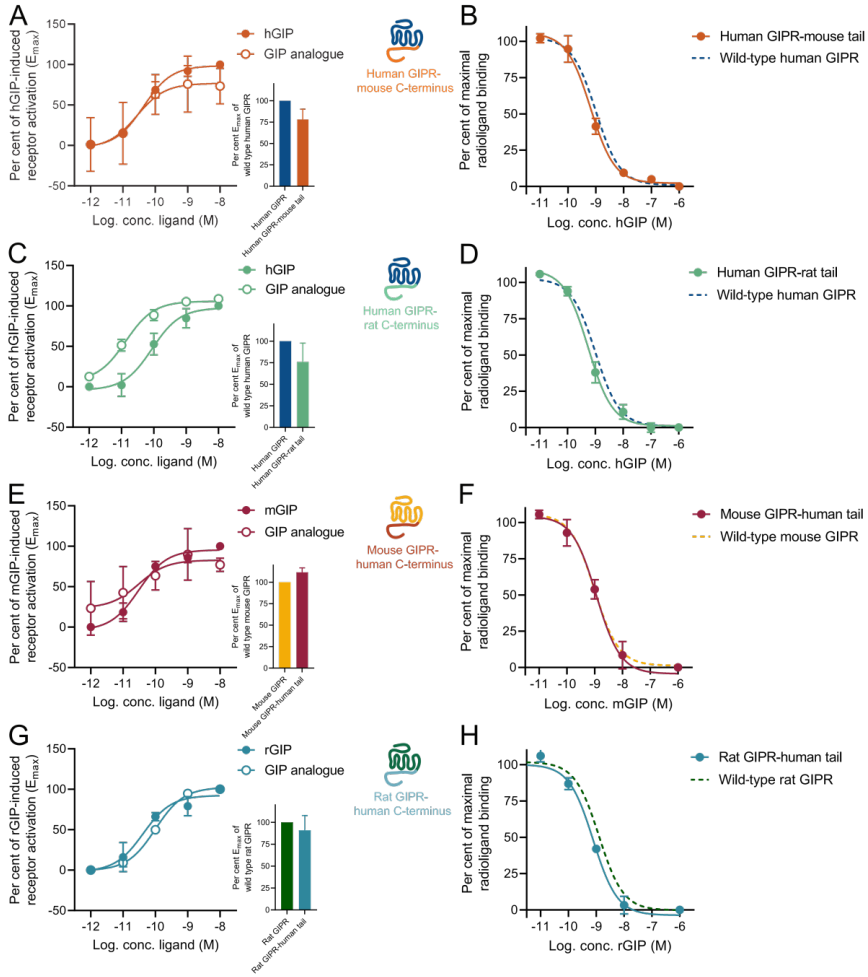
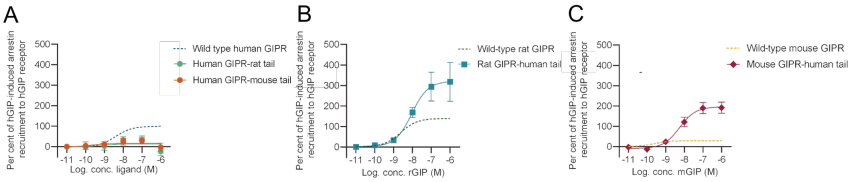
	1	18	30	42
Human (homo sapiens):	YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ			
Rat (rattus norvegicus):	YAEGTFISDYSIAMDKI**R**QQDFVNWLLAQKGKKNDWKHN**L**TQ			
Mouse (mus musculus):	YAEGTFISDYSIAMDKI**R**QQDFVNWLLAQ**R**GKKNDWKHNITQ			
Pig (sus scrofa):	YAEGTFISDYSIAMDKI**R**QQDFVNWLLAQKGKK**S**DWKHNITQ			
Dog (canis lupus familiaris):	YAEGTFISDYSIAMDKI**R**QQDFVNWLLAQKGKKNDWKHNITQ			
Cat (felis catus):	YAEGTFISDYSIAMDKI**R**QQDFVNWLLAQKGKKNDWKHNITQ			

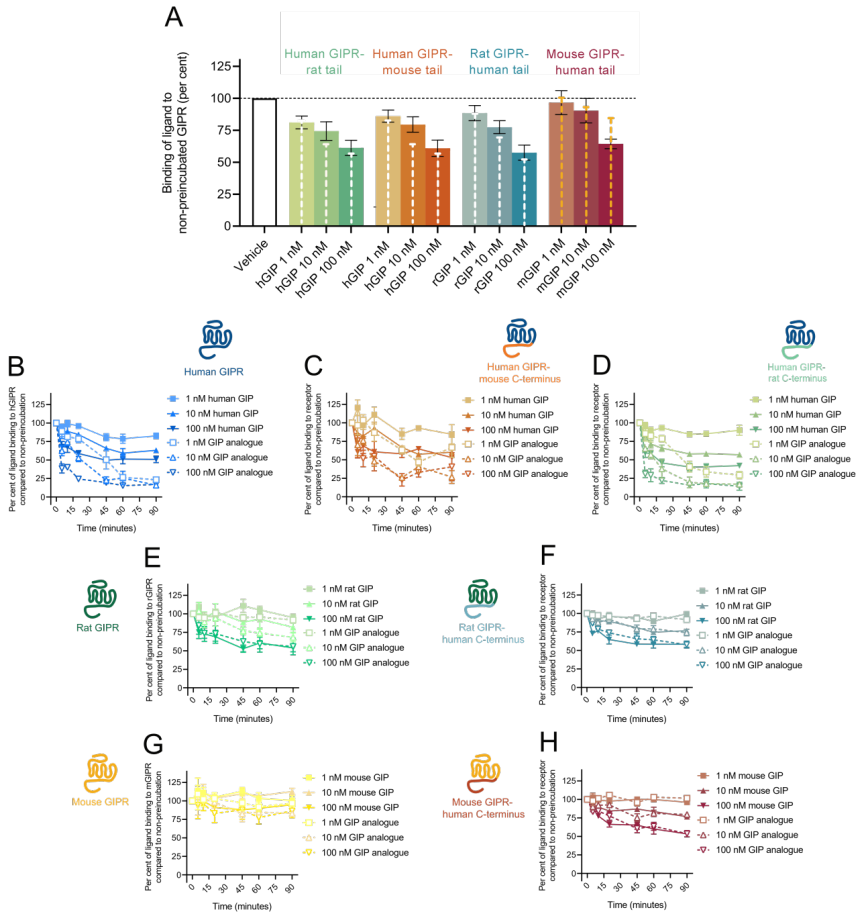












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