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REPLY TO LETTER

Reply to comment on: A second trigeminal CGRP receptor: function and expression of the AMY1 receptor

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In their comment, Haanes et al., suggest that CGRP could act through two distinct receptors in human coronary arteries; namely the CGRP receptor (CLR/RAMP1) and the AMY_1 receptor (CTR/RAMP1).[1] Although there are other possible explanations, the presence of multiple CGRP receptor subtypes could explain their elegant data. In light of the active clinical development of blocking antibodies and small molecules against either CGRP or CLR/RAMP1, this interesting proposition warrants further investigation.

Although Haanes et al., are correct that IUPHAR does not officially recognize a single molecular entity named as the "$CGRP_2$ receptor," the numerous pharmacological activities of CGRP and its receptor heterogeneity are well documented in IUPHAR publications, following-on from initial observations by Remi Quirion, Ian Marshall, David Poyner, Patrick Sexton, and coworkers.[2,3]

The first amylin receptor studies following the discovery of RAMPs showed that αCGRP and amylin could equivalently displace ^{125}I-amylin from the AMY_1 receptor (CTR/RAMP1).[4,5] It was subsequently noted that the '$CGRP_2$' subtype was likely the AMY_1 receptor with possible contributions also by the AMY_3 (CTR/RAMP3) and AM_2 (CLR/RAMP3) receptors, depending on species.[6] However, the excitement surrounding the discovery of amylin receptors appears to have eclipsed wide acknowledgment of the activity of CGRP at the AMY_1 receptor.

We believe that the hormone which physiologically activates the AMY_1 receptor is likely to be dependent upon the access amylin or CGRP has to this receptor. For example, the AMY_1 receptor could act as a receptor for CGRP in trigeminal ganglia, whereas in one or more of the circumventricular organs the AMY_1 receptor could instead be activated by blood-borne amylin.[7,8] As Haanes et al. suggest from their coronary artery data, CGRP also likely has access to AMY_1 receptors at other sites, which could include inside the central nervous system.

The implications of two CGRP receptors for the development of antimigraine treatments is difficult to predict based on current clinical evidence. There are many factors which can effect a drug's in vivo efficacy that are not apparent from cell or tissue-based pharmacological assays. For example, drug binding to plasma proteins, half-life, and distribution to the site (or sites) of action. Consequently clinical data for a single drug, such as AMG 334, is unlikely to conclusively show the value of targeting one receptor over the other. If AMG 334 is truly selective for the CGRP receptor over the AMY_1 receptor the data will be extremely interesting. The recently published study of AMG 334 pharmacology is a positive step forward in characterizing this agent but it does not rule out activity at the AMY_1 receptor[9]. Shi et al., report that calcitonin activity was not blocked by AMG 334 in the amylin-responsive MCF-7 cell line. However, based on the literature, these cells may express a mixture of calcitonin and amylin receptor subtypes and therefore it is unclear if a functional AMY_1 receptor is present[10]. Future studies to confirm the activity (or lack of activity) of AMG 334 at the human AMY_1 receptor may be necessary, using CGRP and amylin as ligands. When coupled with complete pharmacology we expect the results of upcoming clinical trials for AMG 334, anti-CGRP antibodies and small molecule antagonists will provide important insight into the roles of CGRP receptors in migraine.

The future for CGRP-based migraine therapies is extremely bright. Any molecule against this target that is ultimately approved for human use will signal the beginning of a new era in migraine treatment, and provide the driving force for complete understanding of CGRP receptor pharmacology.

Conflict of Interest

The authors declare no conflict of interest.

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