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LETTER

# Comment on "A second trigeminal CGRP receptor: function and expression of the AMY1 receptor"

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Dear Editor,

We read with the great interest the recent publication on a second trigeminal CGRP receptor by Walker et al.[1] The authors convincingly present the presence of a functional noncanonical CGRP receptor (AMY1) at neuronal sites in the trigeminal system. The presence of a second CGRP receptor has been debated and although it is not yet recognized by IUPHAR, several reports have previously suggested the presence of more than one CGRP receptor. We have previously published reports on the effect of olcegepant[2] and telcagepant[3] in the human coronary artery. In these studies, we evaluated several concentra-

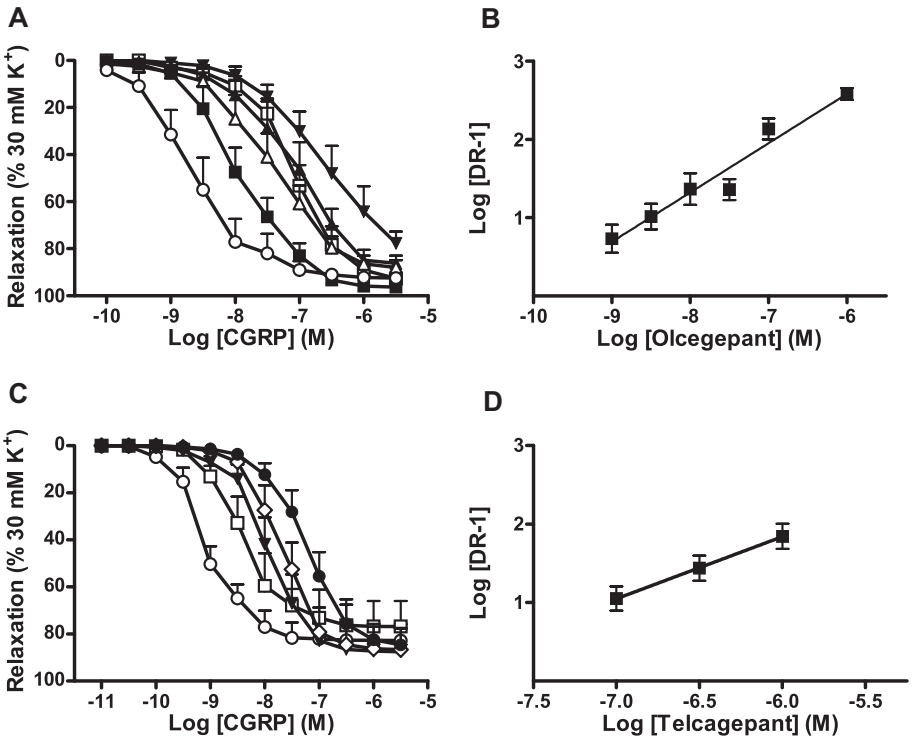


**Figure 1.** Left panels: Relaxant effect of h-αCGRP on human distal coronary arteries in the absence (*open circle*) or presence (*closed square*, 1 nmol/L; *open triangle*, 3 nmol/L; *closed triangle*, 10 nmol/L; *open square*, 30 nmol/L; *closed nabla*, 100 nmol/L; *open diamond*, 300 nmol/L; *closed circle*, 1 μmol/L) of increasing concentrations of olcegepant (A) or telcagepant (C). Right panels: Average Schild plots of the corresponding concentration response curves. The Schild plot slope for olcegepant (B) is 0.68 ± 0.07, which is significantly less than unity, and has a biphasic appearance. The Schild plot slope for telcagepant (D) is 0.8 ± 0.1, and is not statistically different from unity. Only concentrations of antagonist that induced a significant shift in the concentration response curves to CGRP were included in the Schild plot. For more details on the methods, see the original publications.[2,3]

tions of both antagonists and observed clear differences in their respective Schild plots (Fig. 1).

According to the study by Walker et al., olcegepant should discriminate better between hCLR/RAMP1 ("CGRP receptor") and hCTR/RAMP1 ("AMY1 receptor") than telcagepant. This is remarkably similar to what we have observed on the CGRP responses in human isolated distal coronary artery, where the Schild plot slope of olcegepant was significantly different from unity, with a clearly biphasic antagonistic profile,[2] while the Schild plot slope of telcagepant in this same preparation was not significantly different from unity and the antagonistic profile was not that apparent biphasic.[3] This difference can be explained by the presence of two different CGRP receptors for which olcegepant and telcagepant have different affinities. In light of these new experiments on the cloned human receptors, it is even more convincing to us that the human coronary artery also expresses two functional CGRP receptors, most probably matching the presence of hCLR/RAMP1 and hCTR/RAMP1. It is in this setting relevant to mention that amylin indeed causes relaxation in human coronary arteries.[4]

The study by Walker et al. sheds further light on an additional CGRP receptor, which might have implications in migraine in view of therapeutic efficacy and combined with our studies, in view of cardiovascular side effects of CGRP-blocking drugs. As pointed by Walker et al., the clinically studied doses of neither olcegepant nor telcagepant are selective for one these receptors. The CGRP receptor antibody (AMG334), however, selectively binds to hCLR/RAMP1 and not to hCTR/RAMP1.[5] We are awaiting the results of the clinical trials with this antibody with great interest to learn whether this selectivity has any clinical implications.

## Conflict of Interest

The authors are currently characterizing the effects of the antibody AMG344 in the human coronary artery, for which a small grant was received. Amgen is not involved in, neither aware of, the preparation of this comment. The work described in this comment was supported by VIDI grant 91711349 of the Netherlands Organisation for Scientific Research to Antoinette MaassenVanDenBrink and Kristian A. Haanes was supported by a fellowship from the International Headache Society.

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