

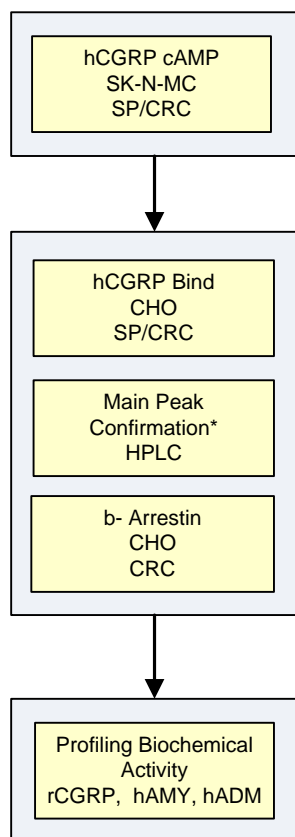
Neuroscience – Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonist

CGRP is a 37 amino acid neuropeptide that plays a key role in the patho-physiology of migraine. CGRP levels in venous plasma have been reported to be elevated during a migraine attack and are normalized after successful treatment of the migraine with a triptan (Goadsby & Edvinsson, 1994). Infusion of CGRP into individuals with a past history of migraine attacks can induce an attack, and CGRP receptor antagonists have successfully treated migraine attacks. As such, we are interested in the identification of novel, non-peptide CGRP receptor antagonists for the treatment of migraine attacks and other disorders. The CGRP cAMP assay tests for compounds that inhibit the activation of the CGRP receptor and the resulting generation of cAMP by CGRP. The active molecules will be further characterized for their ability to inhibit the activity of calcitonin, amylin and adrenomedullin at receptors that respond to these molecules. Compounds of interest will selectively block the CGRP receptor and not have a biological effect at the calcitonin, amylin or adrenomedullin receptors.

- Ana Recobera and Andrew F. Russob; "Calcitonin gene-related peptide: an update on the biology", *Current Opinion in Neurology*, 22:241–246, (2009)
- Ernst ter Haar et al; "Crystal Structure of the Ectodomain Complex of the CGRP Receptor, a Class-B GPCR, Reveals the Site of Drug Antagonism"; *Structure*, 18(9): 1083-1093, (2010)

Flow Scheme & Assay Measures

Neuroscience: CGRP Receptor Antagonist



CGRP Receptor Antagonist

Primary Assays

hCGRP cAMP antagonist SK-N-MC cells SP (% Inhibition)
hCGRP cAMP antagonist SK-N-MC cells CRC (IC₅₀)

Secondary Assays

hCGRP Bndg CRC SK-N-MC cells SP/CRC (%Efficacy) / (IC₅₀)
Main peak confirmation HPLC
hCGRP β- Arrestin CHO cells CRC (IC₅₀)

Confirmatory Assay

Profiling Biochemical Activity rCGRP (spleen homo), hCT, hAMY, hADM Bndg
SPA CHO CRC (Ki)

SP= Single Point

CRC= Concentration Response Curve

Note*: Single Peak purification for active confirmation