Discovery of New Antagonists for TRPM8 Channel by High Throughput Assay

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TRP ion channels family is represented by 85 members that can be organized by their sequence homology into seven subfamilies. Some members of these subfamilies play an important role in detecting temperature changes.

Within TRPV (vanilloid) subfamily, TRPV1 is the most studied member, and has been related with chronic pain, furthermore its pharmacological blockade and genetic deletion experiments have validated TRPV1 as a therapeutic target. Another member of the TRP family is TRPA1, which is activated by noxious cold and chemical compounds including allyl isothiocyanate (AITC), the pungent principle of wasabi and other mustard oils. TRPA1 appears to have a central role in the pain response but also it has been demonstrated that is essential for asthma [1]. TRP melastatin 8 (TRPM8) is activated by chemical cooling agents (such as menthol) or by temperatures between 28-15 ºC, mediating the detection of innocuous cold thermal stimuli. TRPM8 expression up-regulates has been suggested to play an important role in carcinogenesis and related with prostate cancer [2].

In this study was evaluated the biological activity of a new chemical library, through high throughput screening. We report here the identification of compounds presented a high blockade activity on TRPM8 and share common structure. These hits with notorious antagonistic effect were selected and observed in patch-clamp experiments performed in stable cell lines that expressed TRPV1, TRPM8 and TRPA1 to characterize more accurately their properties.

These new pharmacophoric scaffolds can be used as a hit to develop new compounds with better modulator properties interesting to the clinical field or as a research tool.

REFERENCES

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