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Identification of odorant molecules as novel CB1 receptor ligands through *in silico* approach

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INTRODUCTION

- ✓ The CB1 endocannabinoid system is one of the main systems involved in the regulation of dietary intake^{1,2}

Ligands of the CB1 receptor : **CB1 agonists**

↳ induce food intake

CB1 antagonists

↳ decrease food intake and suppress appetite

- ✓ CB1 receptor expression: the CB1 receptor is expressed in the brain and in a number of peripheral tissues in mammals; a CB1-like receptor has also been localized in the olfactory epithelium of *Xenopus laevis* tadpoles³

- ✓ Aroma perception has recently been shown to be implicated in the process of satiety⁴

↳ These findings led us to hypothesize that odorant molecules could have an impact on food intake through interactions with the endocannabinoid system

Aims of the study

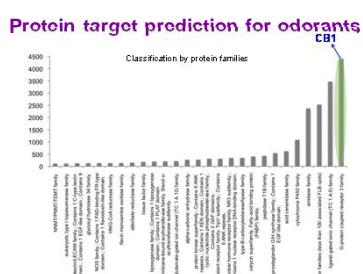
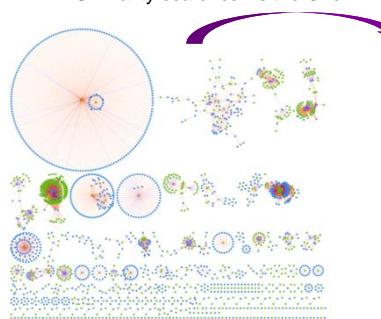
- ❖ to identify odorant molecules that could interact with the CB1 receptor using *in silico* and *in vitro* approaches

Chemogenomic study

Using around 3000 odorant molecules described in the Flavor-Base (Leffingwell & Assoc. <http://www.leffingwell.com/>)

Network pharmacology

- ↳ Mapping the odorant pharmacological space: odor-drug associations
- Structural fingerprints
- Similarity searches vs the ChemProt database^{5,6}

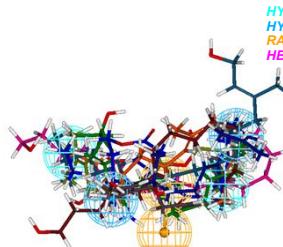


In silico screening

- ↳ Mapping on agonist and antagonist Catalyst/HypGen (Accelrys) models obtained on the basis of literature data^{7,8}

Agonist model

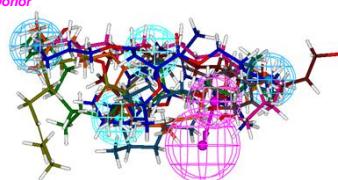
2 HY, 2 HYAL, 1 RA,
correl.=0.99, cost=47, fixed cost=44.5, null cost=237, config=15



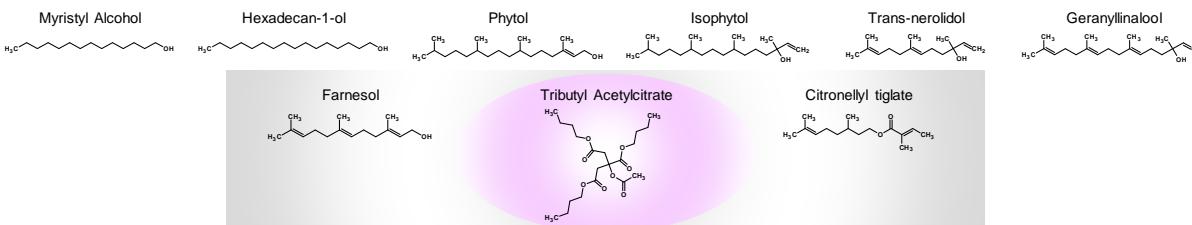
✓ small sphere corresponds to the center of Hydrogen Bond Donor
✓ large sphere is the projection sphere corresponding to a Hydrogen Bond Donor on the receptor site

Antagonist model

2 HY, 2 HYAL, 1 HBD,
correl.=0.98, cost=75, fixed cost=67, null cost=243, config=15

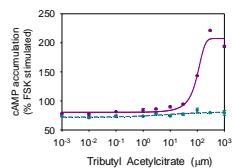
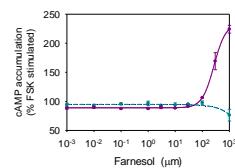
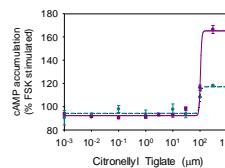


Chemical structures of molecules predicted to be CB1 ligands

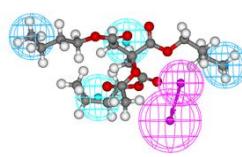


In vitro assays

- three molecules are inverse agonists of the CB1 receptor *in vitro*
best activity obtained with Tributyl Acetylcitrate



Human HEK293 cells were cotransfected with a plasmid encoding the mouse CB1 receptor cDNA and with a plasmid encoding an engineered cAMP sensitive luciferase (Promega). After incubation with the substrate of luciferase, forskolin (1 μM) then the odorant molecules were injected and the luminescence was recorded for 30 min on a bioluminescence plate reader.



Alignment of Tributyl Acetylcitrate on CB1 antagonist model

2 HY, 2 HYAL, 1 HBD, correl.=0.98, cost=75, fixed cost=67, null cost=243, config=15

Conclusion and perspectives

- ❖ On the basis of these findings, interactions between the endocannabinoid system and odorant molecules could be proposed as a mechanism involved in the establishment of satiety
- ❖ Three odorant molecules act as CB1 inverse agonists *in vitro*, supporting the possible pharmacological relevance of the newly identified odorant-target relationships

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