

MEETING ABSTRACT

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The predator odor 2,4,5-trimethylthiazoline binds and activates receptor guanylyl cyclase-G to elicit innate defensive responses

Ying-Chi Chao^{1,2*}, Ruey-Bing Yang^{1,2,3}

From 7th International Conference on cGMP Generators, Effectors and Therapeutic Implications
Trier, Germany. 19-21 June 2015

Background

Guanylyl cyclase (GC)-G is the last member of the receptor GC family [1,2]. Our recent studies demonstrated that GC-G expressed in Grueneberg Ganglion (GG) neurons can be activated by cool temperatures to generate ultrasound calls by isolated pups to elicit maternal care [3]. Detecting the semiochemical warnings present in the environment is essential for species survival. The mouse GG is the olfactory subsystem that also detects alarm pheromones (APs) and other structurally-related chemicals involuntarily released by rodent's predators [4,5]. The predator odor 2,4,5-trimethylthiazoline (TMT), a volatile compound originally isolated from the anal secretions of the red fox, induces robust freezing behaviors in mice. TMT shared a similar chemical structure to APs and can activate GG neurons [5]. However, whether TMT can directly bind and stimulate GC-G activity to trigger innate fear responses remains unknown.

Materials and methods

A combination of biochemical and molecular biology methods, Ca²⁺ imaging as well as behavioural studies comparing wild-type and GC-G-knockout (KO) mice was used to elucidate the molecular and biological function of GC-G in transmitting TMT signaling.

Results

We show that GC-G can be stimulated by TMT in both in vivo cellular cGMP accumulation assays and in vitro GC assays with isolated GC-G membranes protein. Furthermore, domain deletion analysis verifies that the extracellular domain of GC-G is required for TMT-induced cGMP

production. A direct interaction with notable affinity between TMT and GC-G extracellular domain was confirmed by time-resolved surface plasmon resonance. HEK-293T cells co-expressing GC-G and the cGMP-activated ion channel CNGA3 respond to TMT via a rapid influx of calcium. In line with these findings, TMT-induced calcium transients in the GG as well as TMT-evoked innate fear behaviors and an increase of serum corticosterone (a stress hormone) were markedly attenuated in the GC-G-KO mice compared to wild-type littermates.

Conclusions

Our data demonstrated for the first time that TMT may be a potential ligand for GC-G receptor and unravelled the molecular interaction involved in the inter-specific olfactory message communication between predators and preys via TMT-GC-G signaling.

Authors' details

¹Molecular Medicine Program, Taiwan International Graduate Program.

²Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan. ³Institute of Pharmacology, School of Medicine, National Yang-Ming University, Taipei, Taiwan.

Published: 2 September 2015

References

1. Kuhn M, Ng CK, Su YH, Kilic A, Mitko D, Bien-Ly N, *et al*: Identification of an orphan guanylate cyclase receptor selectively expressed in mouse testis. *Biochem J* 2004, **379**(Pt 2):385-393.
2. Chao YC, Cheng CJ, Hsieh HT, Lin CC, Chen CC, Yang RB: Guanylate cyclase-G, expressed in the Grueneberg ganglion olfactory subsystem, is activated by bicarbonate. *Biochem J* 2010, **432**(2):267-273.
3. Chao YC, Chen CC, Lin YC, Breer H, Fleischer J, Yang RB: Receptor guanylyl cyclase-G is a novel thermosensory protein activated by cool temperatures. *EMBO J* 2015, **34**(3):294-306.
4. Brechbuhl J, Klaey M, Broillet MC: Grueneberg ganglion cells mediate alarm pheromone detection in mice. *Science* 2008, **321**(5892):1092-1095.

* Correspondence: ycchao@ibms.sinica.edu.tw

¹Molecular Medicine Program, Taiwan International Graduate Program
Full list of author information is available at the end of the article

5. Brechbuhl J, Moine F, Klaey M, Nenniger-Tosato M, Hurni N, Sporkert F, et al: **Mouse alarm pheromone shares structural similarity with predator scents.** *Proc Natl Acad Sci USA* 2013, **110**(12):4762-4767.

doi:10.1186/2050-6511-16-S1-A40

Cite this article as: Chao and Yang: The predator odor 2,4,5-trimethylthiazoline binds and activates receptor guanylyl cyclase-G to elicit innate defensive responses. *BMC Pharmacology and Toxicology* 2015 **16**(Suppl 1):A40.

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