Food components activating TRPA1

TATSUO WATANABE, YUSAKU IWASAKI, KENJI KOBATA, MANABU TANABE, KANAKO KOIZUMI, YUKIKO OKUMURA, YUKO TERADA, MASATAKA NARUKAWA
Graduate School of Nutritional and Environmental Sciences & Global COE Program
University of Shizuoka
52-1 Yada, Suruga-ku, Shizuoka 422-8526
Japan
watanbt@u-shizuoka-ken.ac.jp
http:// sfns.u-shizuoka-ken.ac.jp/foodchem/

Abstract: - We searched for novel agonists of TRPA1 in garlic, mioga, galangal, black pepper, and royal jelly by the use of heterogeneously expressed cells. Mioga contained novel and more potent TRPA1 agonists than allyl isothiocyanate (AITC), most famous TRPA1 agonist from wasabi. Garlic and black pepper included both TRPA1 and TRPV1 agonists. A galangal pungent compound had strong activity to TRPA1. Specific fatty acids in royal jelly were TRPA1 active components. In animal studies Intravenous AITC and cinnamaldehyde injection caused adrenaline secretion in rats. Feeding experiments in mice with high-sucrose and high-fat diet resulted in suppression of visceral fat deposition by adding black pepper extract or piperine or cinnamaldehyde. These results suggest that food components activating TRPA1 may enhance energy metabolism or thermogenesis.

Key-Words: - garlic, mioga, galangal, black pepper, royal jelly, TRPA1, adrenaline, adipose tissue deposition, energy expenditure

1 Introduction

Most famous thermosensitive TRP (transient receptor potential) channel is TRPV1 or capsaicin receptor. TRPV1 is activated not only by temperature (>43°C) and H^+ but also by some food components including capsaicin in hot pepper. Capsaicin enhances energy metabolism through activation of TRPV1. TRP cation channel subfamily A member 1 (TRPA1) is a kind of thermosensitive TRP channel families. TRPA1 is co-expressed with TRPV1 in sensory nerve endings. We hypothesize that TRPA1 activation compounds from foods are candidates for energy metabolism enhancer.

In this study we investigated the activation of TRPA1 by food components from garlic, mioga, galangal, black pepper, and royal jelly, and found that several compounds are more strong agonist than allyl isothiocyanate (AITC). Further, some TRPA1 agonists induced adrenaline secretion in rats and suppressed visceral fat accumulation in mice.

2 Activation of TRPA1 in cultured cells

Stable Chinese hamster ovarian (CHO) or human embryonic kidney (HEK) 293 cell lines expressing full length human TRPA1 was generated using tetracycline inducible T-REx™ expression system from Invtrogen. Intracellular Ca^{2+} concentration was measured by FlexStation II™ (Molecular Device, USA). In 96-well plates, cells were seeded and cultured. By adding tetracycline, TRPA1 expression was induced. After loading Fluo-4 AM (Ca^{2+} indicator) to cells, sample solutions were added to cells and changes of fluorescence was monitored continuously.

Three diallyl sulfides (Fig. 1) in garlic activated TRPA1 significantly. Diallyl trisulfide showed higher activity (EC_{50} = 0.49 μM) than AITC (EC_{50} = 1.4 μM). Diallyl sulfide and diallyl disulfide were less active than AITC (EC_{50} = 254 and 7.55 μM, respectively) [1]. They were partial agonist for TRPV1 having EC_{50} values around 100 μM [1].

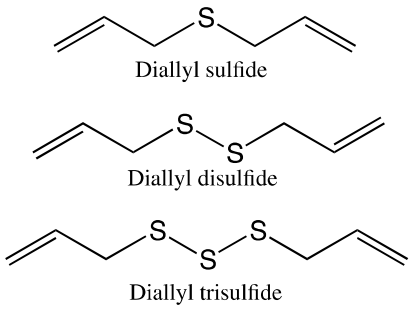


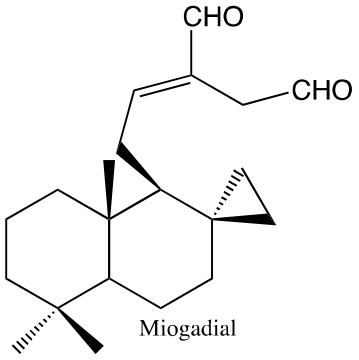
Fig. 1 Chemical structures of allyl sulfides

Mioga (*Zingiber mioga*) or Japanese ginger belongs to *Zingiberaceae*. Pungent compounds in mioga having α,β-unsaturated 1,4-dialdehyde moieties were tested for TRPA1 activity. Like diallyl trisulfide miogadial and miogatrial (Fig. 2) showed higher affinity than AITC [2]. They also activated

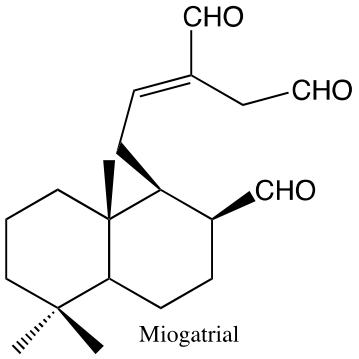
TRPV1 but the affinity was low (10 times higher EC_{50} than those for TRPA1) and the maximum responses were smaller than half of that to capsaicin [2].

Galangal (*Alpinia galanga*) is also a member of *Zingiberaceae*. 1'-Acetoxychavicol acetate (ACA, Fig. 3) is a pungent component in galangal but it is not clear how the pungency of ACA is induced. We clarified that ACA is not TRPV1 but TRPA1 agonist having higher affinity (EC_{50} = 0.16 μM) than AITC [3].

On black pepper, 6 compounds of 19 components activated both TRPA1 and TRPV1 [4]. Piperine and its isomers had higher affinity for TRPV1 than TRPA1. Piperine analogs having longer alkyl chain relatively strongly activated TRPA1.



Miogadial



Miogatrial

Fig. 2 Chemical structures of pungent compounds in mioga

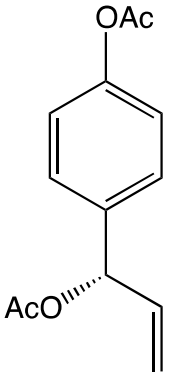
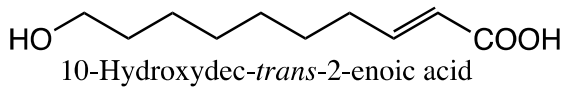
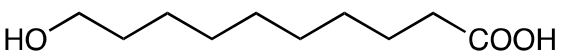


Fig. 3 Chemical structures of ACA



10-Hydroxydec-*trans*-2-enoic acid



10-Hydroxydecanoic acid

Fig. 4 Chemical structures of major hydroxy fatty acids found in royal jelly

Further, we searched for TRPA1 activity in royal jelly. We found that hydroxyl fatty acids (Fig. 4), specific components in royal jelly, were TRPA1 agonists with 100 times larger EC_{50} values than AITC and partial TRPV1 agonists of the same EC_{50} values [5].

3 Animal experiments

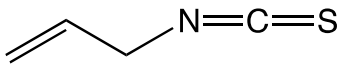
To show the possibility that TRPA1 agonist could enhance energy metabolism, 2 kinds of animal experiments were performed.

Adrenaline response to food components was measured in blood from the adrenal vein of anesthetized rats [6].

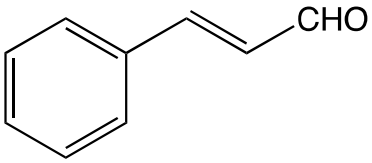
Effect of food components on visceral fat accumulation in mice fed high-fat and high-sucrose diet was also evaluated as an in vivo test [7].

The intravenous administration of AITC (1 – 10 mg/kg) or cinnamaldehyde (CNA, 5 or 10 mg/kg), both of which are famous TRPA1 agonist, induced adrenaline secretion. These responses were blocked by cholinergic blockers, showing the participation of adrenal sympathetic nerve activity. Further, capsaicin-treatment, which impairs sensory nerve function, abolished fully the response due to AITC or CNA. These results suggest that TRPA1 agonists induce adrenaline secretion via sensory nerve activation [6].

Two feeding experiments were carried out. One was for black pepper extracts or piperine and the other was for CNA. Feeding high-fat and high-sucrose (HFS) diet for 1 month induced obesity in C57BL mice. By adding 0.03 or 0.05% of piperine or black pepper extract containing same amount of piperine, the deposition of visceral fats were abolished and UCP1 contents in interscapular brown adipose tissue increased [7]. Also CNA feeding to HFS diet inhibited the accumulation of visceral fats at least due to brown adipose tissue activation.



Allyl isothiocyanate



Cinnamaldehyde

Fig. 5 Chemical structures of AITC and CNA

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4 Conclusion

These results suggest that TRPA1 agonists may enhance energy metabolism in part through adrenaline release from the adrenal gland and sympathetic nerve activation in brown adipose tissue similar to capsaicin's action mechanism for energy metabolism enhancement [8].

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