ショウガオールは出血性脳障害に対して神経保護効果を発揮するがギンゲロールにはその効果がない：ヘムオキシゲナーゼ -1 の発現誘導への a, b- 不飽和カルボニル構造の寄与

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Shogaol but not gingerol has a neuroprotective effect on hemorrhagic brain injury: contribution of the α, β-unsaturated carbonyl to heme oxygenase-1 expression

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ABSTRACT: We investigated the effects of shogaol, which has an α,β-unsaturated carbonyl group, and gingerol, which does not, on primary-cultured microglia to understand how the α,β-unsaturated carbonyl interacts with Kelch-like ECH-associated protein (Keap)1. Shogaol (1 μM) but not the same concentration of gingerol significantly increased heme oxygenase (HO)-1 protein levels in cultured microglia without cytotoxicity. In addition, shogaol suppressed the release of the inflammation marker nitric oxide induced by 30 U/ml thrombin treatment. A docking simulation suggested that the α,β-unsaturated carbonyl of shogaol but not gingerol interacts with Keap1. Nuclear import of nuclear factor E2-related factor 2 and increased binding of the HO-1 E2 enhancer support the docking-simulation prediction. The transcription inhibitor actinomycin D (0.1 μg/ml) markedly blocked the increase of HO-1 mRNA levels by shogaol. To evaluate whether the α,β-unsaturated carbonyl can be used for intracerebral hemorrhage (ICH) therapy, we investigated the effect of shogaol on an in vivo mouse ICH model. Intracerebroventricular injection of 0.2 nmol shogaol increased striatal HO-1 protein levels and rescued ICH-induced neuron loss. Thus, the α,β-unsaturated carbonyl is necessary for the interaction of compounds, such as shogaol, with Keap1, and these findings may be useful for screening novel ICH therapeutic agents that increase HO-1 expression.

抄録　抗酸化酵素 HO-1 の誘導に寄与する Keap1 と相互作用しうる化学構造として α,β-不飽和カルボニルに着目し、分子内にそれを持つショウガオールと持たないギンゲロー

ルの作用の差について初代培養ミクログリアを用いた検討を行なった。その結果、ショウガオールのみが Keap1 から転写因子 Nrf2 を遊離・核内移行し、ARE 配列を介した HO-1 の発現を誘導した。ショウガオールは、in vivo 脳出血モデルでもミクログリアにおける HO-1 誘導に基づく抗炎症作用を示し、神経保護効果を発揮した。