

感覚創薬：TRPA1作動性匂い分子による人工冬眠・生命保護状態誘導原理に基づく革新的創薬技術

プロジェクト
責任者

関西医科大学 附属生命医学研究所

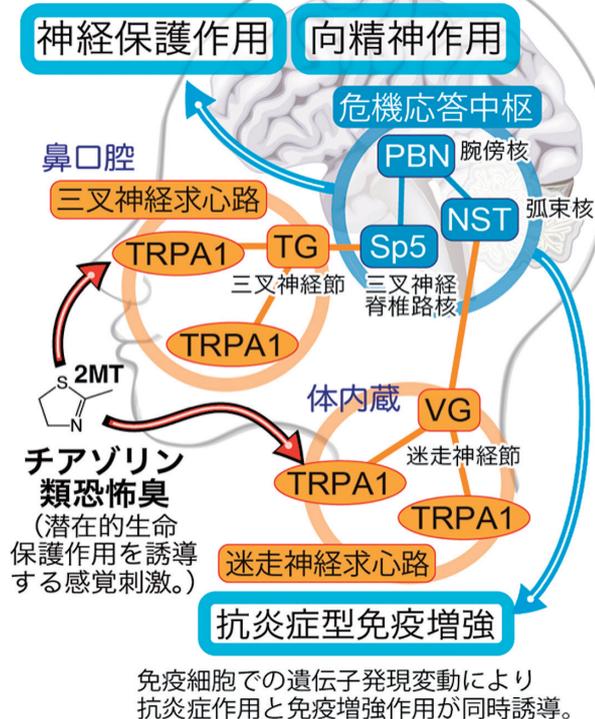
准教授 小早川 高

プロジェクト概要

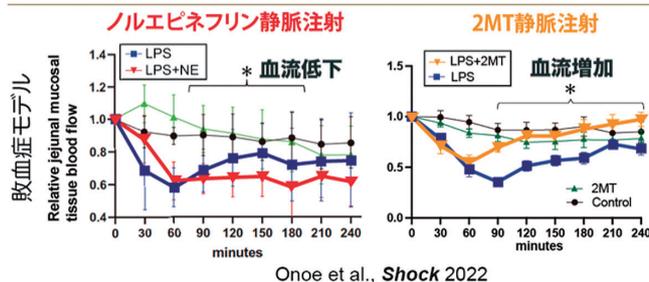
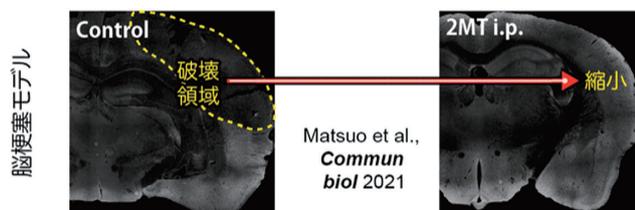
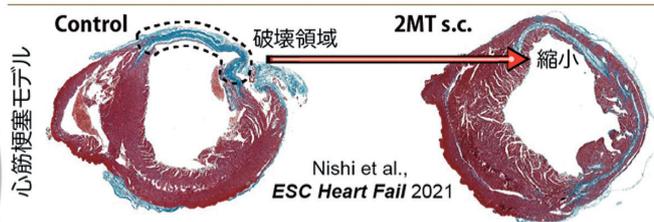
生物は潜在的な生命保護能力を進化させ生存競争を生き抜いた。生命保護能力の全貌は不明であり、また、それら能力を人為的に誘導する医薬品は未開発である。先天的恐怖情動は危機状態での生存確率を上昇させる生体反応を統合指揮する脳機能として進化したと考えられる。これら生命保護と先天的恐怖情動の進化的な関連から、何らかの感覚刺激が先天的恐怖情動の制御システムへ情報を伝達することで、潜在的な生命保護作用が誘導される可能性がある。

私たちは、この仮説に基づき、先天的恐怖情動システムに人為的に介入し、生死を決する潜在的な生命保護作用を誘導する感覚刺激とその受容体の組み合わせを初めて発見した。三叉・迷走神経のTRPA1をチアゾリン類恐怖臭で活性化すると、脳の危機応答中枢が活性化され、その結果、致命的な低酸素環境や敗血症状態での生存率が劇的に上昇する「人工冬眠・生命保護状態」が誘導できる。本研究開発では、適切なTRPA1作動性感覚刺激を利用して潜在的な保護作用を誘導する感覚創薬技術を利用し、敗血症、ARDS、脳梗塞などの救急疾患治療薬や臓器保存薬などを開発している。

感覚創薬概念図



病態モデルでの治療効果



COVID-19などの炎症性感染症の治療には、免疫増強と抗炎症作用の同時誘導が望ましいが、このような薬効を持つ医薬品は未開発である。チアゾリン類匂い分子刺激は、脳を介して免疫細胞の遺伝子発現を調節する作用を持つため、自然免疫の強化と抗炎症作用の同時誘導を可能にする。感覚創薬では匂い分子吸入以外にも静脈注射や経口投与などが利用でき、様々な疾患治療に応用できる。本技術の実用化のため、製薬や化学企業、匂い分子の新たな利用法の開発や臓器保存技術の開発を目指す企業などとのパートナーシップを進めたい。

Sensory medicine: Innovative therapeutics based on the principle of inducing the artificial hibernation / life-protective state by TRPA1 - activating odor molecules

Principal Investigator

Kansai Medical University

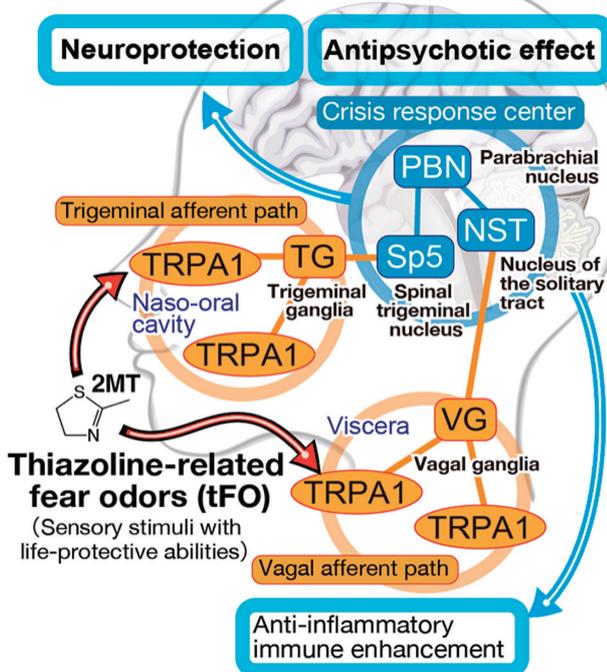
Associate Professor Ko KOBAYAKAWA

Project Outline

Organisms have evolved latent life-protective capabilities and survived the race for existence. The whole picture of these life-protective abilities is unknown, and the drugs that artificially induce these abilities have yet to be developed. Innate fear is thought to have evolved as a function of the brain that integrates physiological responses to increase the chance of survival in crisis situations. Given the evolutionary link between life-protective abilities and innate fear emotions, it is hypothesized that some sensory stimuli may induce latent life-protective effects by transmitting information to the central regulatory system of innate fear emotions in the brain.

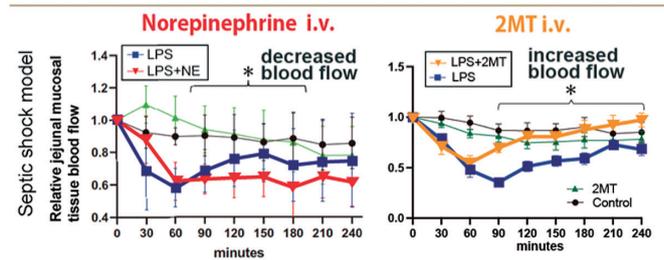
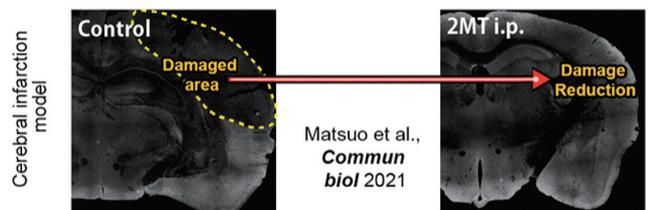
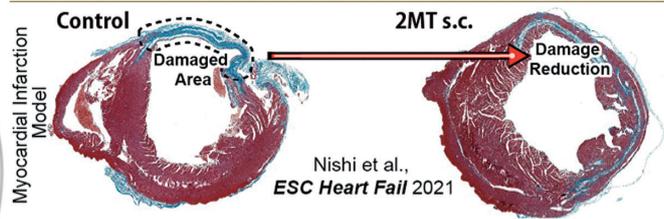
Based on this hypothesis, we have discovered combinations of odor molecules and their receptor that artificially interfere with the innate fear system to induce life-protective effects that can determine life-or-death in critical situations. Activation of TRPA1 in the trigeminal and vagus nerves with thiazoline-related odor molecules activated the central crisis pathway in the brain, resulting in life-protective effects, including a dramatic increase in survival rate in a lethal hypoxic environment and in septic conditions. In this research and development, we are developing emergency drugs for sepsis, ARDS, ischemia-reperfusion injury, etc., and organ preservation drugs by using "sensory medicine" technology, a method to induce innate fear-induced life-protective effects through sensory stimulation.

Conceptual Diagram of Sensory Medicine



Alterations of gene expression in the innate immune cells lead to simultaneous enhancement of innate immunity and anti-inflammation abilities.

Effect of treatment in pathological models



Simultaneous induction of immune-enhancing and anti-inflammatory effects is desirable for the treatment of inflammatory infections such as COVID-19, but drugs with such medicinal properties have yet to be developed. Thiazoline-related odorants modulate gene expression of immune cells through the brain circuit to enable simultaneous induction of innate immunity enhancement and anti-inflammatory effects. Sensory medicine utilizes a new route of drug administration, in which drugs are delivered in the nasal cavity as odors, and can be applied to treat various diseases. In order to put this technology to practical use, we would like to promote partnerships with pharmaceutical manufacturers, companies that develop functional gas generators, and companies that develop organ preservatives.