令和 7 年度　第 21 回　大学院セミナー

令和 7 年 6 月 17 日

分 野 名 Area of Research (責任者名)(内線)	内臓機能生理学分野 責任者名(　井上　剛　)　　内線(　7031　)
演　　題 Title	**Harnessing Therapeutic Ultrasound to Attenuate Acute Kidney Injury**
講 師 等 Presenter	Mark D. Okusa 先生 バージニア大学医学部・教授
概要 Abstract	The inflammatory reflex is a neural circuit that regulates the body's immune response to pathogens and tissue injury. The afferent arc is activated by cytokines and it transmits signals to the brain through the afferent vagus nerve which leads to activation of the efferent or motor limb resulting in suppression of inflammation. Multiple methods have been used to activate this pathway leading to reduced inflammation in various diseases such as colitis1, sepsis,2,3 rheumatoid arthritis,4 acute lung injury,5-7 diabetes,8 and obesity.9 We have demonstrated that electrical VNS,10,11 optogenetic VNS stimulation,10 and pulsed ultrasound (US)12-14 can activate the CAP to reduce inflammation and kidney injury in acute kidney injury (AKI). Activation of the CAP was implicated in the mechanism of protection by demonstrating the abolishment of protection in splenectomized mice and in mice lacking α7nAChRs. Furthermore, adoptive transfer of VNS conditioned α7nAChR splenocytes to naïve mice conferred protection. Optogenetics was used to further refine our understanding of the specific neural circuits involved.15 Anterograde efferent fiber stimulation and anterograde sensory afferent fiber stimulation both conferred protection from AKI while retrograde stimulation did not. Pulsed ultrasound, through CAP activation, similarly demonstrated a protective effect from the development of ischemic AKI. Specifically, bursts of ultrasound delivered 24 hours prior to IRI reduced inflammation and improved renal function after AKI. While the ability of ultrasound to modulate the CAP to protect against AKI has been clearly demonstrated, the origin of these effects is unclear. Mechanotransduction is the process by which mechanical stimuli are converted into electrical or chemical signals.16 Mechanosensitive ion channels sense position, movement, touch, pressure and pain and enable cells to transduce mechanical stimuli into electrochemical signals.17 The mechanical force from ultrasound opens these channels, inducing downstream signaling processes, eventually lead to changes in cellular behavior and the subsequent biological effects. The goal of our studies is to understand how the biomechanical effect of pulsed ultrasound (pUS) is transduced into biochemical signals to activate the inflammatory reflex pathway thereby blocking inflammation and acute kidney injury (AKI) and kidney fibrosis of chronic kidney diseases (CKD). We believe that pUS activates mechanosensory channels. 1. Nunes NS, Chandran P, Sundby M, et al. Therapeutic ultrasound attenuates DSS-induced colitis through the cholinergic anti-inflammatory pathway. EBioMedicine 2019;45:495–510. DOI: 10.1016/j.ebiom.2019.06.033. 2. Gigliotti JC, Huang L, Bajwa A, et al. Ultrasound Modulates the Splenic Neuroimmune Axis in Attenuating AKI. J Am Soc Nephrol 2015;26:2407–2481. DOI: 10.1681/ASN.2014080769.

	3. Gigliotti JC, Huang L, Ye H, et al. Ultrasound prevents renal ischemia-reperfusion injury by stimulating the splenic cholinergic anti-inflammatory pathway. J Am Soc Nephrol 2013;24(9):1451–60. DOI: 10.1681/ASN.2013010084. 4. McAllen RM, Cook AD, Khiew HW, Martelli D, Hamilton JA. The interface between cholinergic pathways and the immune system and its relevance to arthritis. Arthritis Res Ther 2015;17:87. DOI: 10.1186/s13075-015-0597-2. 5. Yamada M, Ichinose M. The cholinergic anti-inflammatory pathway: an innovative treatment strategy for respiratory diseases and their comorbidities. Curr Opin Pharmacol 2018;40:18–25. DOI: 10.1016/j.coph.2017.12.003. 6. Su X, Lee JW, Matthay ZA, et al. Activation of the alpha7 nAChR reduces acid-induced acute lung injury in mice and rats. Am J Respir Cell Mol Biol 2007;37(2):186–92. DOI: 10.1165/rcmb.2006-0240OC. 7. Su X, Matthay MA, Malik AB. Requisite role of the cholinergic alpha7 nicotinic acetylcholine receptor pathway in suppressing Gram-negative sepsis-induced acute lung inflammatory injury. J Immunol 2010;184(1):401–10. DOI: 10.4049/jimmunol.0901808. 8. Wang L, Opland D, Tsai S, et al. Pten deletion in RIP-Cre neurons protects against type 2 diabetes by activating the anti-inflammatory reflex. Nat Med 2014;20(5):484–92. DOI: 10.1038/nm.3527. 9. Xie H, Yepuri N, Meng Q, et al. Therapeutic potential of alpha7 nicotinic acetylcholine receptor agonists to combat obesity, diabetes, and inflammation. Rev Endocr Metab Disord 2020;21(4):431–447. DOI: 10.1007/s11154-020-09584-3. 10. Tanaka S, Abe C, Abbott SB, et al. Vagus nerve stimulation activates two distinct neuroimmune circuits converging in the spleen to protect mice from kidney injury. Proc Nat Acad Sci 2021;118(12). 11. Inoue T, Abe C, Sun-sang JS, et al. Vagus nerve stimulation mediates protection from kidney ischemia-reperfusion injury through α7nAChR+ splenocytes. J Clin Invest 2016;126(5):1939–1952. 12. Inoue T, Abe C, Kohro T, et al. Non-canonical cholinergic anti-inflammatory pathway-mediated activation of peritoneal macrophages induces Hes1 and blocks ischemia/reperfusion injury in the kidney. Kidney Int 2019;95(3):563–576. 13. Gigliotti JC, Huang L, Bajwa A, et al. Ultrasound modulates the splenic neuroimmune axis in attenuating AKI. J Am Soc Nephrol 2015;26(10):2470–2481. 14. Gigliotti JC, Huang L, Ye H, et al. Ultrasound prevents renal ischemia-reperfusion injury by stimulating the splenic cholinergic anti-inflammatory pathway. J Am Soc Nephrol 2013;24(9):1451–1460. 15. Tanaka S, Okusa MD. Optogenetics in understanding mechanisms of acute kidney injury. Nephron 2018;140(2):152–155. 16. Mofrad MR, Kamm RD. Cellular mechanotransduction: diverse perspectives from molecules to tissues: Cambridge University Press, 2009. 17. Chalfie M. Neurosensory mechanotransduction. Nature Rev Mol Cell Biol 2009;10(1):44–52.
開催日時 Date and Time	令和 7 年 6 月 24 日（火） 10:00 ～ 11:00
開催方法 Online/Face to face	対面：医学部ポンペ会館セミナー室
備考 Notes	

■先端医療科学特論（基礎編）　□先端医療科学特論（臨床編）
□先端新興感染症病態制御学特論　□先端放射線医療科学特論
□日本語（Japanese）　■英語（English）
■対面（Face to face）　□オンライン(Online)