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Risks of Impaired Organ Protection with Inhibiting Transient Receptor Potential Vanilloid 1 (RE: Garami A, et al. 2017[Nov]; 127: 813–23)

Yu Wu, M.D.[1,2], **Eric R. Gross, M.D., Ph.D.**[1], and **Jinqiao Qian, M.D., Ph.D.**[1,3]

[1]Department of Anesthesiology, Perioperative and Pain Medicine, School of Medicine, Stanford University, Stanford, CA, 94305, U.S.A

[2]Department of Anesthesiology, Second Affiliated Hospital of Anhui Medical University, Hefei, China

[3]Department of Anesthesiology, the First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province 650032, China

To the editor

With great interest we recently read the manuscript by Garami *et al.*,[1] illustrating how the transient receptor potential vanilloid 1 (TRPV1) antagonists, AMG 517 and ABT-102, prevent anesthesia-induced hypothermia and simultaneously decrease opioid requirements for postoperative hyperalgesia in rodents. These preclinical data suggest that TRPV1 antagonists may be useful as opioid-sparing modalities for analgesia intraoperatively and postoperatively while also providing hyperthermia to pharmacologically counteract anesthetic-induced hypothermia. This finding is pretty novel and may lead the way to developing new opioid sparing drugs to be used perioperatively. However, it would be of benefit if the authors may comment on some of the potential shortcomings we see of using TRPV1 antagonists during surgery and potential strategies to overcome these barriers we outline below.

For example, intravenous administration of TRPV1 antagonists may also block endogenous mechanisms of organ protection. It is important to recognize that untreated TRPV1 knockout mice or mice treated with a TRPV1 inhibitor subjected to ischemia-reperfusion injury using an isolated heart model produce impaired functional recovery compared to wild type (WT) TRPV1 mice.[2] Further, in a deoxycorticosterone acetate (DOCA)-salt hypertension model, ablation of TRPV1 gene in the C57BL/6 mice exacerbates renal damage compared to

Corresponding Author: Jinqiao Qian, Mailing address: Department of Anesthesiology, the First Affiliated Hospital of Kunming Medical University, Kunming, Yunnan Province 650032, China, Phone number: 8613669723435, qianjinqiao@126.com.

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Not applicable

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Not applicable

Conflicts of Interest
ERG holds a US patent titled "*Peptide Modulators of Specific Calcineurin Protein-protein Interactions*". There are no conflicts of interest to declare.

DOCA-salt-treated WT mice, indicating that TRPV1 may constitute a protective mechanism against end-organ damage induced by hypertension.[3] Additionally, TRPV1 channel activation reduces organ injury for the lung,[4] kidney[5] and brain.[6] Further, TRPV1 antagonists may interfere with the agents or interventions administered perioperatively that may decrease organ injury, such as a surgical incision or opioids that appear to provide their protective effect by a TRPV1-dependent mechanism.[7] Therefore, using TRPV1 antagonists for surgeries undergoing organ reperfusion injury or in a patient population with cardiovascular disease that are at higher risk of having an intraoperative myocardial infarction may possibly cause an unwanted side effect of exacerbating organ injury during ischemia-reperfusion or block the abilities for agents we commonly administer in the operating room to limit cellular injury.

Hypothermia induced by TRPV1 activation is also considered as a promising intervention for organ protection. Rinvanil, a TRPV1 agonist, induces mild hypothermia (33°C), which is associated with 34 % smaller cerebral infarct size volumes in mice subjected to transient middle cerebral artery occlusion versus vehicle treated controls.[5] Thus, drugs specifically inhibiting TRPV1 may interrupt the benefits of hypothermia associated with organ protection.

In conclusion, it is important to consider whether blocking TRPV1 to reduce opioid requirements or raise body temperature may have some unknown risks.

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