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Naringin relieves diabetic cardiac autonomic neuropathy mediated by purinergic $P2Y_{14}$ receptor overexpression in glial cells of superior cervical ganglion

Introduction: Diabetic cardiac autonomic neuropathy is one of the most prevalent complications of diabetes, however there are no treatments to help patients suffering from this heart dysfunction. This manuscript used a traditional Chinese medicine naringin that was proven to improve signs of cardiac autonomic neuropathy. They identified an effect of it in the superior cervical ganglia (SCG) of diabetic rats. The data outlined below emphasize the importance of the peripheral nervous system in heart dysfunction and suggest a mechanism involving purinergic neurotransmitters in glial cells offering new perspectives in the development of the disease and treatments.
Methods: They used rat males that they fed with a diet rich in high fat, high sugar diet in addition to the use of streptozotocin (STZ) to establish a diabetic rat model. They treated these rats with naringin or a short hairpin RNA (shRNA) to knock-down $P2Y_{14}$. They phenotyped rats for signs of cardiac autonomic neuropathy including blood pressure, heart rate variability and sympathetic nerve discharge. They evaluated $P2Y_{14}$ signaling in the SCG using western-blot, immunofluorescence, and ROS levels were measured. Finally, they also evaluated the docking between naringin and $P2Y_{14}$ using molecular docking computations.
Results: They identified that $P2Y_{14}$ was expressed in glial cells of the SCG. Then they observed that the use of P2Y14, shRNA or naringin blunted in part the change in heart function and structure induced by high fat high sucrose-STZ treatment. They harvested the SCG and observed that the increase in IL-1β and ROS levels in the SCG of diabetic rats were reduced with P2Y14 shRNA treatment. Then they observed in silico that naringin was potentially capable of binding the P2Y receptor via hydrogen bond on five unique amino acids.
Conclusions: Using their model and treatments, the authors confirmed that when rats are treated with high fat high carbohydrate/STZ, the SCG get overactivated. This sympathetic overactivation may lead to neuropathy of nerves innervating the heart resulting in cardiac damage. They showed that treatment with naringin or knockdown of P2Y14 may rescue or delay the pathology.

Comment. This paper is interesting since it confirms that inflammation/P2Y signaling and likely overactivation of the peripheral nervous system may be one of the roots of cardiac dysfunction in diabetes. It stresses the fact to pursuing longitudinal research on these topics may contribute to better understand the pathology of cardiac autonomic neuropathy and develop specific drugs targeting these sympathetic ganglia. While this paper is interesting, more data would help to specify mechanisms and timeline of effects, including longitudinal and cell-specific data. Indeed, whole tissues were processed at the end of the treatments, naringin and shRNA treatments were systemic, so it is not clear whether the conclusion related to the role of P2R14 in glial cells is highly relevant while intriguing. Obviously, one challenge is to verify this knowledge in humans, and it is important to note that just males were used here.

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Reference. Tang G, Pi L, Guo H, Hu Z, Zhou C, Hu Q, Peng H, Xiao Z, Zhang Z, Wang M, Peng T, Huang J, Liang S, Li G. Naringin Relieves Diabetic Cardiac Autonomic Neuropathy Mediated by $P2Y_{14}$ Receptor in Superior Cervical Ganglion. Front Pharmacol. 2022 Apr 21;13:873090. doi: 10.3389/fphar.2022.873090. https://www.frontiersin.org/articles/10.3389/fphar.2022.873090/full