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Body Temperature Sensor, TRPM2, Involving in the Regulation of Metabolism.

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Summary

TRPM2 is a thermosensitive non-selective cation channel expressed in various tissues including brain, spleen and pancreatic β-cells where TRPM2 is continuously affected by core body temperature. TRPM2 activity at body temperature could be regulated along with metabolic state because its activity is affected by intracellular factors reflecting cellular metabolism such as NAD^+ metabolites, Ca^{2+} and redox signal. Therefore, TRPM2 is suggested to function as body temperature/metabolic sensor.

Additional metabolic sensor, SIRT1, is a NAD^+-dependent enzyme to regulate energy homeostasis and longevity, etc. Because SIRT1 generates o-acetyl adenosine diphosphate ribose（OAADPR）, a TRPM2 activator, along with its enzymatic activity, this study has focused functional coupling of TRPM2/SIRT1, and their involvement in the regulation of metabolism and b-cell functions.

Pancreatic β-cells functionally express SIRT1, and SIRT1 activator（SRT1720）enhances Ca^{2+} oscillation in β-cell, suggesting that SIRT1 activity elevates insulin secretion. Immunoprecipitation studies have clarified physical interaction between TRPM2 and SIRT1 which is enhanced by phorbol ester（PMA）-treatment. Analysis of phosphoproteins using phos-tag SDS-PAGE has shown that PMA-treatment also increases TRPM2 phosphorylation, suggesting that PKC-mediated phosphorylation of TRPM2 enables effective coupling of TRPM2 and SIRT1. Moreover, whole-cell patch-clamp study has revealed TRPM2 activation by SRT1720.

These results indicate PKC activation down stream of several receptor activation could modify TRPM2 activity at body temperature. Future studies will reveal the physiological functions of TRPM2/SIRT1 coupling in the regulation of metabolism and insulin secretion.