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The Glycemia Control by a Specific Inhibitor of Vesicular Nucleotide Transporter

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Summary

Vesicular nucleotide transporter (VNUT) is responsible for vesicular storage of ATP, and is essential for purinergic chemical transmission. ATP transport activity is driven by the membrane potential ($\Delta\psi$), and allosterically regulated by Cl^-. *VNUT*$^{-/-}$ mice showed improvement of the major factors involved in lifestyle-related diseases despite no change in phenotype. Therefore, specific inhibitors of VNUT may be useful lead compounds for the development of therapeutic drugs.

Extensive screening identified a specific inhibitor of VNUT with IC_{50} of 15.6 nM, which acts as an allosteric modulator through competition with Cl^-. The compound selectively and reversibly inhibited vesicular ATP release from ATP-releasing cells. *In vivo*, we examined the effects of VNUT inhibitor on glycemia control and inflammatory pain using wild-type and *VNUT*$^{-/-}$ mice. The VNUT inhibitor attenuated chronic nociceptive pain and inflammation without affecting basal pain perception in wild-type but not *VNUT*$^{-/-}$ mice. The analgesic effect against chronic inflammatory pain was stronger than that of acetaminophen (a widely used NSAID) and diclofenac (a strong NSAID in clinical use). The VNUT inhibitor showed enhanced glucose tolerance and insulin secretion after oral injection of glucose.

In summary, we identified a specific inhibitor of VNUT that relieves hyperglycemia, inflammatory pain and chronic inflammation without affecting baseline levels. The specific inhibitor of VNUT may represent a new drug for lifestyle-related disease with few side effects.