Novel O-GLcNAcase Inhibitor and Fluorogenic Substrate as a Tool for Diagnosing Type 2 Diabetes

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Technology description

Summary

NIH researchers have synthesized a novel analogue of O-(2-acet-amido-2-deoxy-D-glycopyrano-sylidene)amino-N-phenylcarbamate (PUGNAc), which bears an extension on the N-acetyl moiety. This modified PUGNAc acts as a selective inhibitor of O-GlcNAcase; an enzyme that removes N-acetylglucosamine from nuclear and cytoplasmic proteins, and whose inhibition is associated with the development of Type 2 diabetes. The most desirable feature of this new compound is its ability to specifically inhibit O-GlcNAcase without targeting the related hexosaminidase A (HEX A) and hexoaminidase B (HEX B) enzymes. This unique property distinguishes it from the original PUGNAc and other compounds which inhibit O-GlcNAcase as well as other enzymes. It also has a smaller inhibitory effect on O-GlcNAcase compared to the original PUGNAc. These properties make the modified PUGNAc useful for diagnostic or therapeutic applications involving Type 2 diabetes.
A fluorescent derivative of the modified PUGNAc has also been developed. Modified PUGNAc, conjugated to a fluorescent moiety such as 4-methylumbelliferone, can serve as a substrate for O-GlcNAcase without inhibiting HEX A. This allows the fluorescently labeled compound to be used for measuring O-GlcNAcase enzyme activity, and thus provide a means of diagnosing Type 2 diabetes in human blood or tissue samples. Previous reagents have monitored other Type 2 diabetes related enzymes, but with much less specificity. Recent studies that link mutations of the MGEA5 gene (which codes for O-GlcNAcase) to Type 2 diabetes provide further support for the use of the fluorescent derivative as a potent tool for diagnosing the disease. The fluorogenic derivative may also be used as a novel imaging agent for assessing O-GlcNAcase function in-vivo .

Application area

Diagnosis of type 2 diabetes
In vivo imaging of O-GlcNAcase enzyme function

Institution

NIH - National Institutes of Health

联系我们

叶先生

电 话：021-65679356

手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com