Gadofullerene Nanoparticles

in the treatment of Type 2 Diabetes by improving Pancreas Dysfunctions

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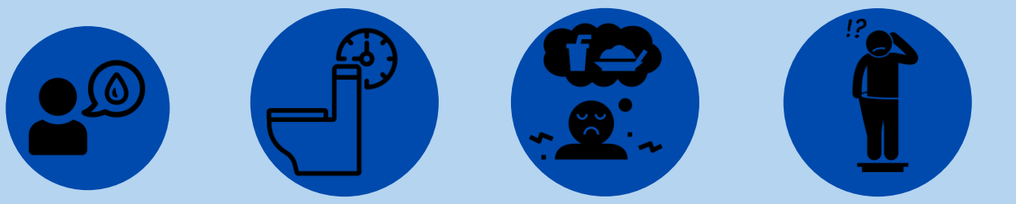
Abstract

Type 2 diabetes mellitus (T2DM) has been one of the most prevalent metabolic disorders. Nonetheless, the commonly used anti-T2DM drugs failed to substant to treat T2DM when anti-T2DM was withdrawn. Here we put forward a superior and sustainable anti-diabetic strategy using intraperitoneal administration of amino-acid-functionalized gadofullerene nanoparticles (GFNPs) in db/db diabetic mice. Highly accumulated in the pancreas and liver, GFNPs could prominently decrease hyperglycemia, along with permanently maintaining normal blood sugar levels in T2DM mice and even stopping administration. Importantly, GFNPs reversed the pancreas islets dysfunctions by reducing oxidative stress and inflammation responses and fundamentally normalized the insulin secretory function of the pancreas islets. Mechanistically, GFNPs improved hepatic insulin resistance by regulating glucose and lipid metabolism through the activation of IRS2/PI3K/AKT signal pathways, resulting in inhibiting gluconeogenesis and increasing glycogenesis in the liver. Additionally, GFNPs relieved hepatic steatosis in the liver, ultimately maintaining systemic glucose and lipid metabolic homeostasis without obvious toxicity. Together, GFNPs reverse the dysfunctions of the pancreas and improve hepatic insulin resistance, providing a promising approach for T2DM treatment.

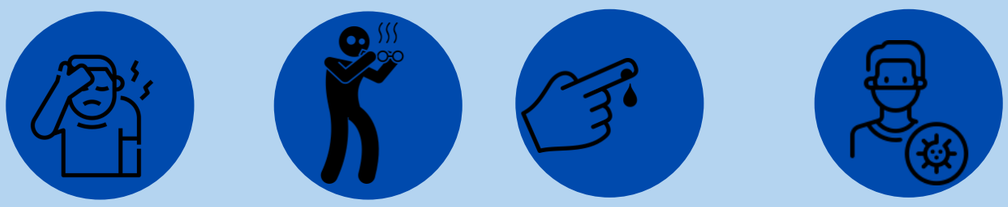
Definition :

Type 2 diabetes is a chronic disease. It is characterized by high levels of sugar in the blood. Type 2 diabetes is also called type 2 diabetes mellitus and adult-onset diabetes. That's because it used to start almost always in the middle- and late-adulthood. However, more and more children and teens are developing this condition.

Symptoms:



Increased thirst | **Frequent urination** | **Increased hunger** | **Unintended weight loss**

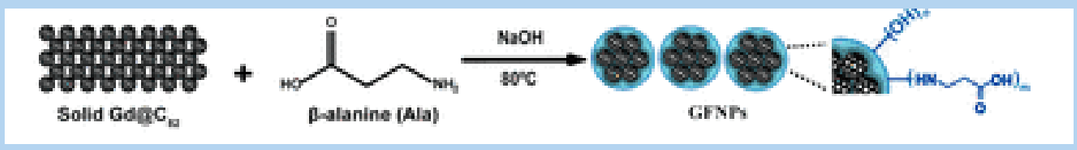


Fatigue | **Blurred vision** | **Slow-healing sores** | **Frequent infections**

Numbness or tingling in the hands or feet

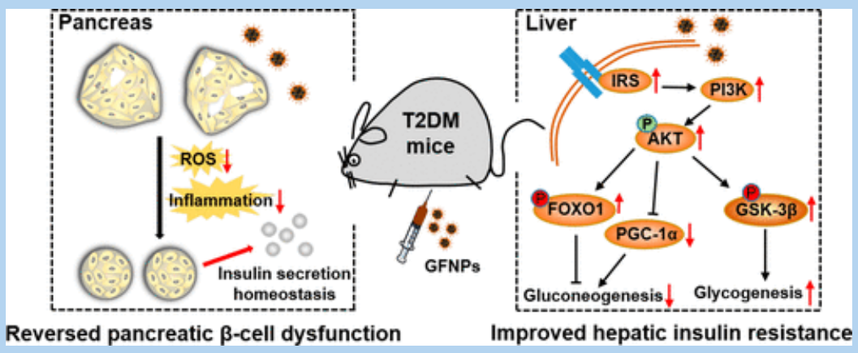
Preparation of GFNP:

The amino acid derivatives of GFNPs were simply prepared via a solid-liquid method in an alkali aqueous solution with β-alanine under a heating condition. The obtained solutions were then purified by dialysis, and the size distribution of GFNPs was evaluated by atomic force microscope (AFM) and dynamic light scattering (DLS). It revealed that GFNPs had an average diameter of ∼60 nm and a height of ∼12 nm.The hydrodynamic diameter of GFNPs was 137.5 ± 2.21 nm, and the ζ potential was approximately −36.5 ± 1.70 mV (Figure 1c). Additionally, the stabilities of GFNPs were examined in simulated physiological conditions, such as in saline, the fetal bovine serum (FBS), and the Dulbecco's modified Eagle medium (DMEM). We could find the stable GFNP solutions in these mediums, even after centrifugation at 9000 rpm for 5 min



How it works:

GFNPs mainly regulated the IRS/PI3K/AKT insulin signal pathway by reversing the pancreatic dysfunctions by reducing oxidative stress and inflammation responses to improve hepatic insulin resistance in diabetic mice. Furthermore, GFNPs could also regulate glucose metabolism, resulting from the inhibition of hepatic gluconeogenesis and the promotion of hepatic glycogenesis via AKT/FOXO1/PGC-1α and AKT/GSK-3β pathways, respectively. In addition, excessive lipid accumulation in liver inducing hepatic steatosis, as a common T2DM complication, is widely believed to be closely associated with hepatic insulin resistance



Experiment:

In diabetic db/db mice, pancreatic β-cells failed to meet the demand of insulin target organs due to the damage from oxidative stress and inflammation induced by hyperglycemia. the main oxido-reductases of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT) in serum were highly decreased in diabetic mice ($P < 0.01$ compared with C57/BL/6J mice), but significantly increased after treatment with GFNPs. The malonaldehyde (MDA) and 4-hydroxy nonenal (4-HNE), two important products of lipid peroxide, were both increased in the serum of db/db mice and deceased after GFNPs treatment suggesting the positive regulation of oxidative stress by GFNPs in diabetic mice. Moreover, the mRNA levels of Sod1, Gpx1, and Cat, measured by quantitative polymerase chain reaction (Q-PCR), in the pancreas were increased due to oxidative stress, and the expressions of those indicators were nearly reversed to normal after GFNP treatment.GFNPs significantly decreased the mRNA expressions of inflammatory factors in the pancreas, such as Nf-kb, Tnf-α, IL-6, and IL-1β, suggesting that GFNPs attenuated the inflammation reaction of the pancreas in diabetic mice.

The advantages of GFNPs treatment for T2DM :

(1) GFNPs could significantly decrease blood glucose of db/db mice back to normal levels and not induce hypoglycemia.

(2) GFNPs realized a sustainability anti-diabetic effect, and there was no rebound in blood sugar after stopping administration of GFNPs.

(3) GFNPs could effectively reduce the overweight of diabetic mice without serious toxicity.

(4) GFNPs could fundamentally reverse the dysfunctions of the pancreas and normalize the morphology and secretory function of pancreatic islets in diabetic mice.

(5) GFNPs reversed diabetic complications and hepatic steatosis, along with anti-T2DM.

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