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Streptozotocin - an antibiotic used to induce diabetes on experimental animals

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Abstract

Streptozotocin (STZ) is a cytostatic antibiotic produced by *Streptomyces achromogenes*. It is an inhibitor of DNA replication showing a special affinity for pancreatic β -cells DNA. It is used in medicine as an antineoplastic agent (indicated in the treatment of malignant neoplasms of pancreas) and in scientific research to induce hyperglycemia, insulinitis, diabetes mellitus (DM), Alzheimer's disease on experimental animals. Insulinopenia syndrome is called 'streptozotocin diabetes', caused by necrosis of the pancreatic β -cells. STZ induced DM offers a very cost-effective and expeditious technique in medical research.

Streptozotocin

History

Streptozotocin (STZ) is a glucosamine-nitrosourea compound, has the molecular formula $C_8H_{15}N_3O_7$. It is a broad-spectrum antibiotic produced by *Streptomyces achromogenes*. Scientists from a drug company Upjohn in Kalamazoo, Michigan discovered it in a strain of soil. The birthplace of STZ is considered to Blue Rapis, Kansas - the soil sample in which the microbe turned up has been taken from there.[1] In the late 1950s it was identified as an antibiotic. In the mid-1960s, STZ was found to be toxic to the beta cells of the pancreatic islets.[2] This suggested the drug's use as an animal model of diabetes and as a medical treatment for β -cells cancer.[3,4] Since then, for more than 50 years STZ became the most frequently studied experimental model of DM.[5] In 1982 Food and Drug Administration (FDA) approved STZ for treating pancreatic islet cell cancer - the drug was marketed as Zanosar®.

β -cell selectivity

STZ is classified as nitrosourea analogue because it contains N-methyl-N-nitrosourea (MNU) moiety linked to hexose. Its toxicity could be achieved only after intracellular transport. Due to nitrosoureas lipophilic properties, transportation of STZ to cells is fast. As a glucose analog STZ is selective transported into pancreas β -cells by glucose transport protein 2 (GLUT2). That explains its toxicity to β -cells.[6] Cells without expression of this transporter are resistant to STZ. The toxic action is not only specific to the pancreas. STZ can damage other organs that expresses GLUT2, including kidneys, liver and brain.[4,7] This observation can confirm significance of transporter.[8]

β -cell toxicity

STZ has toxic properties because it contains methylnitrosourea moiety that causes DNA alkylation. Transfer of the methyl group leads to DNA damage and fragmentation. It induces intracellular DNA repair systems, and poly ADP-ribose polymerase (PARP) overstimulation. That causes a deficit of energy stores (NAD^+ , ATP) and finally necrosis of β -cells.[9,10] The DNA methylation process can be suppressed by PARP inhibitors. Injection of PARP inhibitor protects β -cells against the toxic of STZ and prevents the development of a diabetic state.[5] Absence of PARP prevents the depletion of NAD cofactor, loss of ATP and death cell consequence. For example in spite of DNA fragmentation, mice are resistant to β -cells death mediated by STZ because of PARP deficient.[5,9,10].

There is a theory that STZ induces diabetes because of its action as intracellular nitric oxide (NO) donor rather than DNA alkylation. Nitroso group is a compound of STZ and MNU and it can release NO. STZ can also stimulate guanylyl cyclase, thereby production of cGMP that is the same result as NO provides.

Inhibition of insulin secretion

STZ inhibits insulin secretion and causes insulin dependent diabetes mellitus. Influence of STZ on insulin and glucose homeostasis is an effect of its toxicity for β -cells. It has an impact on insulin production, secretion, and glucose metabolism. STZ does not cause direct suppression of glucose transport or phosphorylation, although it can be observed later, when β -cells are damaged and gene expression is altered.

Before visible effects of DNA damage, synthesis of insulin could be lower because of decreased NAD⁺ levels. At the next stage insulin secretion is impaired through failure of mitochondrial enzymes and damage of their genome. Study from 1989 confirmed this theory showing protection of β -cells function by nicotinamide (inhibitor of DNA repair mechanism PARP) pre-treatment at early stages of STZ administration. Those protective properties of nicotinamide failed after longer STZ exposure.[11]

Summary

STZ is the main chemical agent of choice used in scientific research for reproducible induction of diabetes in experimental animals. The mechanism of β -cells necrosis was investigated and is quite well understood. Streptozotocin (STZ) is transported via selective β -cell transport (GLUT2) and causes alkylation of DNA. DNA damage induces activation of poly ADP-ribose polymerase (PARP) that leads to depletion of cellular NAD⁺ and ATP. That causes β -cell death – necrosis. In result insulin dependent DM and chemical (STZ) diabetes - a very cost-effective and expeditious technique in medical research.[6]

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