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Anti-Covid Drug: 2-deoxy-D-glucose and Its Mechanism of Action

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Abstract

2-deoxy-D-glucose (2-DG) is a glucose analogue that has been found very effective for therapeutic use as an antiviral agent against SARS-CoV-2. This glucose analogue enters into the cell like a glucose molecule. In the cytosol, it is phosphorylated to 2-deoxy-D-glucose-6-phosphate by the action of the enzyme hexokinase. The 2-deoxy-D-glucose-6-phosphate cannot be further metabolized by phosphor-glucose isomerase, which leads to the accumulation of 2-DG-P in the cell and the depletion in cellular ATP. So the cell activates the cell death pathway. The Drugs Controller General of India (DCGI) has approved for emergency use as an adjunct therapy in moderate to severe Coronavirus patients. The drug will help to save precious lives by the faster recovery of hospitalized patients and reducing oxygen dependence. It will lower down the burden on the health infrastructure of the country.

Introduction

On 8th May, 2021, the Drugs Controller General of India (DCGI) has approved 2-deoxy-D-glucose (2-DG) for emergency use in symptomatic Covid-19 patients. It is a modified glucose molecule that has been found to have some therapeutic values as an anti-cancer and antiviral agent against SARS-CoV-2. This drug has been developed jointly by the Institute of Nuclear Medicine and Allied Sciences (DRDO-INMAS) and Dr Reddy's Laboratories (DRL), Hyderabad. This molecule helps in the faster recovery of hospitalized patients and reduces supplemental oxygen dependence. A higher proportion of patients treated with 2-DG showed RT-PCR negative conversion in COVID patients. The drug will be of immense benefit to the people suffering from COVID-19.

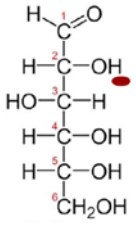
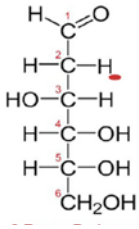
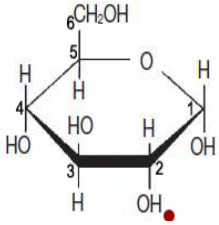
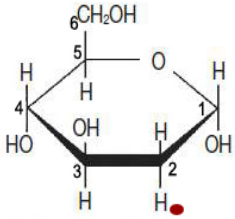
Comparison between Glucose and 2-deoxy-D-glucose (2-DG)

2-deoxy-D-glucose (2-DG) is a glucose analogue and a novel molecule. Previously, it is also used in other purposes such as diagnostic use in pet scanning, anti-cancer therapy. It is a modified glucose molecule in which one hydroxyl group at carbon atom (C-2) is replaced by hydrogen so that it cannot undergo further glycolysis. As such, it acts to competitively inhibit the production of glucose-6-phosphate from glucose at the phosphoglucoisomerase level. 2-DG is uptaken by the glucose transporters of the cell. The comparison between D-glucose and 2-Desoxy-D-glucose is given in Table 1.

Mechanism of Action of 2-deoxy-D-glucose (2-DG)

Viruses clearly rely on host cell machinery for its multiplication. Viral infection triggers metabolic reprogramming in host cells to facilitate increased virus

Table 1: Comparison between D-glucose and 2-deoxy-D-glucose

Sl. No.	Particulars	D-glucose	2-deoxy-D-glucose
1	Molecular formula	C6H12O6	C6H12O5
2	Molecular structure (Fischer projections) – open structure	 D-glucose	 2-deoxy-D-glucose
3	Molecular structure (Haworth projections)- Ring structure	 D-glucose	 2-deoxy-D-glucose
4	Functional group at 2nd carbon atom	Glucose molecule has a hydroxyl group in carbon atom (C-2).	It is a glucose molecule that has a hydrogen atom in the carbon atom (C-2) in place of the hydroxyl group.
5	Number of the hydroxyl group	Five hydroxyl groups	Four hydroxyl groups
6	Molecular weight	180.16 g	164.16 g
7	Function	Normal glycolysis process carried in the cell releasing energy in the form of ATP.	It causes the inhibition of the glycolysis process, thereby preventing energy production in the form of ATP.
8	Use	Source of energy for the cell.	Used as an anti-Covid drug.

multiplication. Different viruses rewire host cell metabolism to facilitate optimal viral replication. Several viruses up-regulate consumption of key nutrients like glucose, glutamine for their needs. Glucose is the most common source of cellular energy and a substrate for many biochemical processes. Each cell needs glucose as universal fuel. Glucose is a hydrophilic molecule and needs the help of the transporter to get into the cell. Inside the cell, glucose enters and goes through various cycles like glycolysis to produce energy in the form of ATPs.

Similarly, 2-deoxy-D-glucose (2-DG) enters into the cell with the help of the transporter and enters into the glycolysis cycle partially. In the glycolysis process, glucose converted into glucose-6-phosphate by the hexokinase enzyme. Similarly, by hexokinase enzyme phosphorylated the 2-deoxy-D-glucose at the 6th carbon atom converting it to 2-deoxy-D-glucose-6-phosphate. However, 2-deoxy-D-glucose-6-phosphate does not undergo further reaction by a glycolytic pathway which is usually driven by the phospho glucose isomerase enzyme. This enzyme does not convert 2-DG into fructose-6-phosphate, leading to the accumulation of 2-deoxy-D-glucose-6-phosphate in the cytosol. So this will have an inhibitory feedback effect on the hexokinase enzyme, and also, it does not go down into the glycolysis process; thereby, it is going to inhibit glycolysis (Aghaee *et al*., 2012).

It is speculated that SARS-CoV-2 cells exhibit a stress response that activates increased levels of glucose transporter expression and increased glucose uptake. Therefore, cells with higher glucose uptake have also a higher uptake of 2-DG. High intracellular levels of 2-DG-6-PO_4 cause allosteric and competitive inhibition of hexokinase and hexose phosphate isomerase enzymes. So glycolysis process inhibited and thereby, energy stores such as ATP are further depleted and finally, the cell activates the cell death pathway (Aft *et al.,* 2002).

The *in vitro* cell cultures experiment was conducted in a laboratory at the Centre for Cellular and Molecular Biology (CCMB), Hyderabad. The cell cultures without 2-DG had more viral plaques – clear spots indicating cell damage by the virus – compared to the ones with 2-DG (Figure 1).

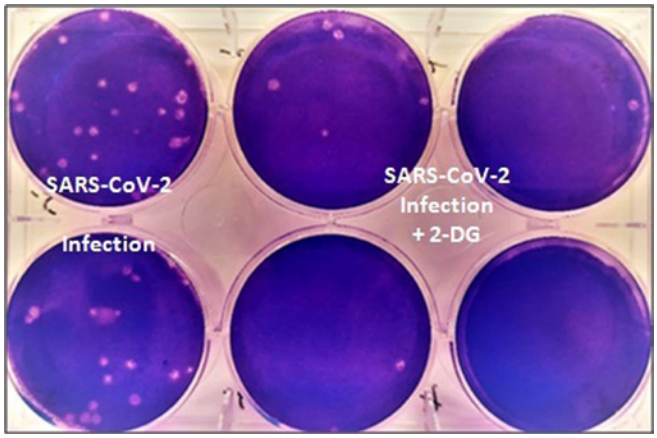


Figure 1: Image of cell cultures in an in vitro study of 2DG [Source: Ministry of Defense/Press Information Bureau (https://pib.gov.in/)]

Conclusion

The indigenous anti-Covid drug '2-deoxy-D-glucose' is one of the first therapeutic molecule which works to stop viral growth in the body, reduce the need for external oxygen. It is a glucose analogue (*i.e.*, not true glucose). It is available in powder form and can be taken orally by dissolving in water. It selectively destroys the virus-infected cells by inhibiting viral growth by hindering viral synthesis and energy production. The emergency approval of the drug came when India is fighting against the Coronavirus that has disrupted healthcare infrastructure across the country.

References

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