Review Article

2-Deoxy Glucose : A Ray of Hope for Treatment of Covid-19

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ABSTRACT

2-Deoxy-D-glucose, mimic of glucose having deoxygenated carbon at second position i.e. hydroxyl group is replaced by hydrogen, due to which 2-DG cannot undergo further glycolysis. It inhibits the production of glucose-6-phosphate from glucose at the phosphoglucoisomerase level which is second step of glycolysis.

Keywords: 2-deoxy glucose, 2-DG, hydrolysis inhibitor, cancer treatment, covid-19 treatment.

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INTRODUCTION

Due to formation and intracellular accumulation of **2**-deoxy-d-glucose-6-phosphate (**2**-DG6P), **2**-**DG** (Figure 2) inhibits glycolysis and inhibits the function of hexokinase and glucose-6-phosphate isomerase. This phenomenon inducing death of cells.

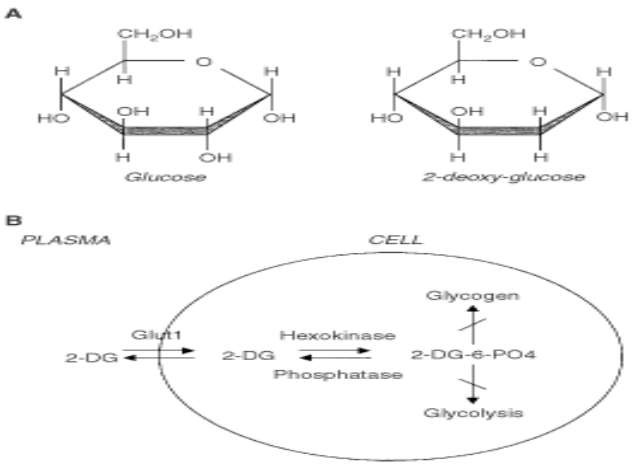

Figure 1(A) Structural comparison of glucose and 2-deoxy-D-glucose. 2DG and glucose differ at the second carbon. (B) Schematic diagram of 2-DG action. 2DG enters the cell through the glucose transporter and is phosphorylated by hexokinase.

Due to low levels of intracellular phosphatase, 2-DG-PO4 is trapped in the cell. 2-DG-PO4 is unable to undergo further metabolism. High intracellular levels of 2-DG-6-PO4 cause allosteric and competitive inhibition of hexokinase. This results in inhibition of glucose metabolism.[2]

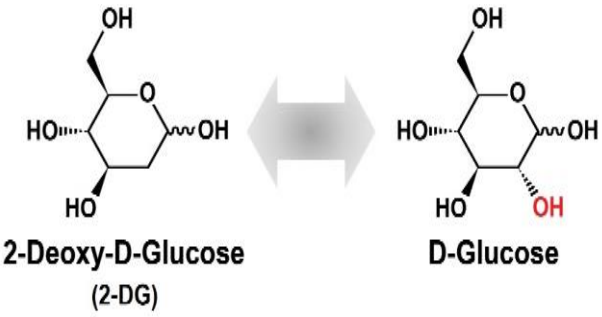

Figure 2: Structures of Glucose and 2-DG

When cancer cells treated with 2-DG it shows higher levels of the Glut1 transporter protein and exhibit increased uptake of glucose, indicating that increased death of cells in response to 2-DG treatment. 2-DG inhibits glycolytic pathway to decrease the viability of tumor cells and also inhibit ATP generation. Cancer cells will decrease as glycolysis has stopped so no new pyruvate is produced and the H+ and NADH are being used in the later stages of respiration while not getting replenished. (Figure 3)

2-DG is up taken by the glucose transporters of the cell so that cells needed higher glucose amount for energy like tumour cells, so that also required higher amount of 2-DG. Since 2-DG inhibits cell growth, it is suggested to be a tumour therapeutic agent.[4]

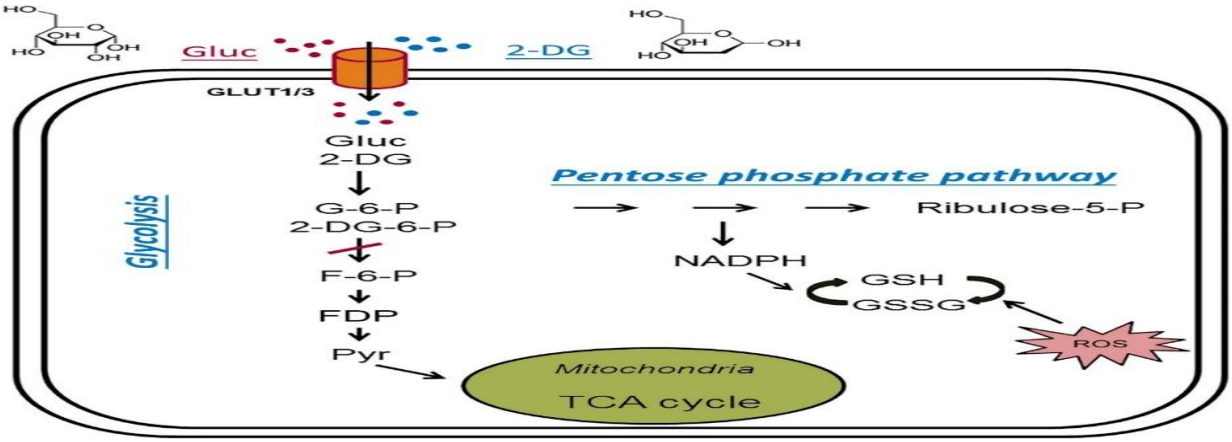

Figure 3: Glycolytic inhibition via 2-DG.[3]

Glycolysis inhibitor used in cancer treatment

2-DG is used as an anticancer and antiviral agent and in the treatment of solid tumours (lung, breast, pancreas, head, neck, and gastric tumours) used as an adjunct to chemotherapy and radiotherapy. (Figure 4)

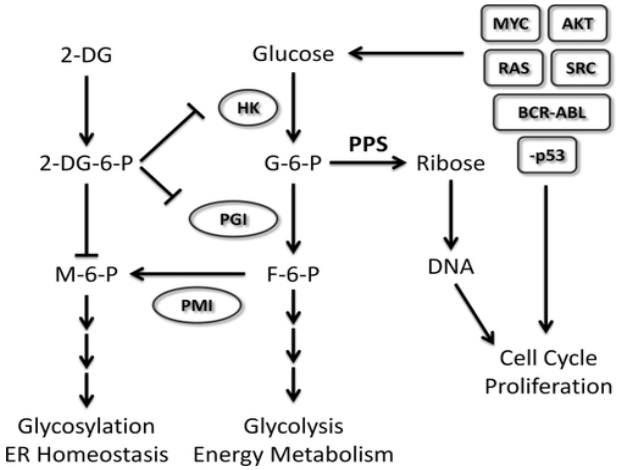

Figure 4: 2-DG exploits a universal trait of cancer.[5]

The mechanism is not completely known that 2-DG inhibits glycolysis and so on cell growth. But this is fact that 2-DG inhibited glycolysis and treated as to stop growing the cells.[6,7] It has structural similarity to mannose, so that 2-DG has the potential to inhibit N-glycosylation, Endoplasmic Reticulum stress and the Unfolded Protein Response pathway.[8,9,10]

As per reported study it is found that by combining the sugar 2-DG with fenofibrate,(a compound used for lowering down cholesterol and esters of glycerol found in blood), the entire tumour could successfully be cured without using critical chemotherapy.[11,12,13]

HeLa cells[14] and yeast showed resistance to 2-DG,[15] which involves the detoxification of a metabolite derived from 2-DG (2-DG-6-phosphate) by a phosphatase. Such a phosphatase is existed in human (named HDHD1A)cells, but yet not clear that it contributes to the resistance of human cells to 2-DG or affects FDG-based imaging.(Figure5)

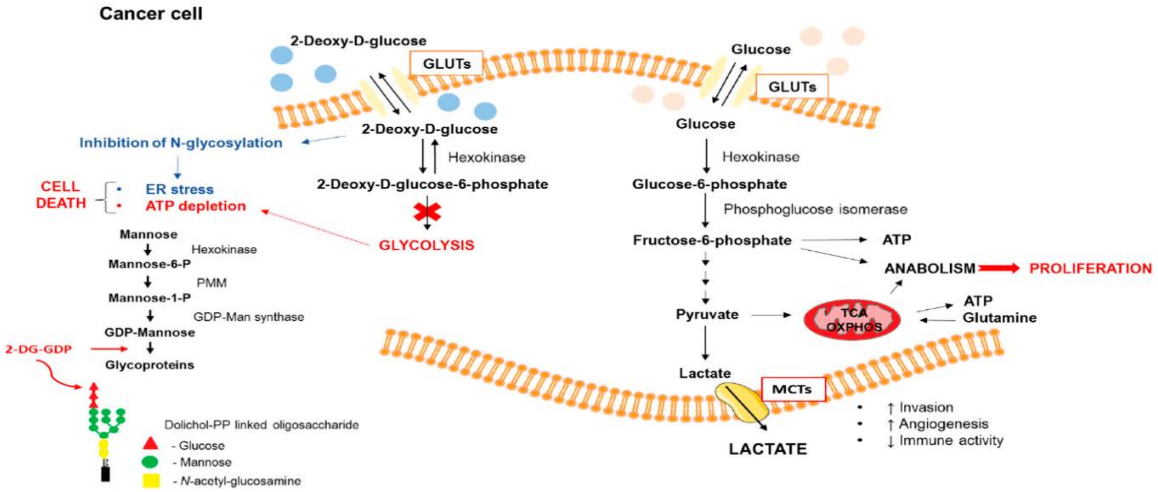

Figure 5: Effect of 2-DG in cancer cell.[16]

In Covid-19 infection

Based on the above mechanism that 2-DG is glycolysis inhibitor and already used for cancer and herpes treatment, scientists developed successful clinical trials for covid-19. (Figure 6)

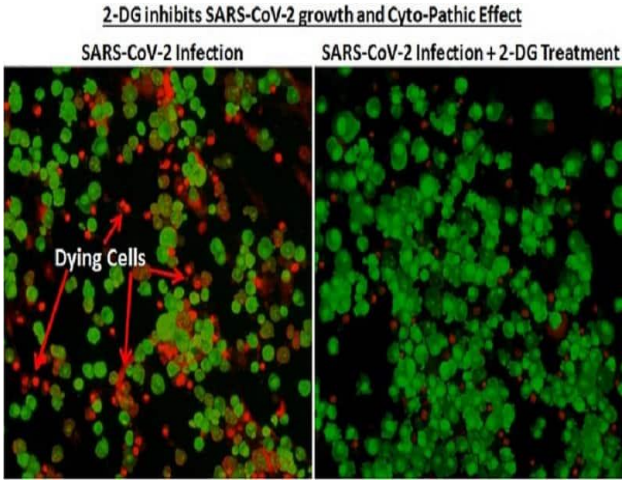

Figure 6: 2-DG effect on SARS-CoV-2 infection

Reports claim that this drug selectively accumulates in infected cells and cuts off the energy supply to the virus. Therefore, the virus cannot multiply automatically, which helps in reducing the infection and the viral load gradually. Eventually, the cells recover and it is selectively taken up by infected cells only. However, it does not specify if this drug has the potential to kill some of the normal cells, or harm them, or has no impact on them whatsoever.

While judging risks and benefits, the most significant thing is to evaluate if the benefits outweigh the risks. Currently, it is being administered to those who have moderate to severe Covid-19 infection. After using this drug, the probability of recovery in these patients is much higher than those put on standard care treatment.

The same is true for antiviral drugs and antibiotics that all these drugs have side-effects, they do affect normal cells, but the damage is much lesser than the benefit that we get out of them.

Broadly, 2-DG can be classified as an antiviral, but in the true sense, it is not an antiviral because it is not killing the virus. It only gets aggregated inside the cell and cuts off the growth material required for the virus to grow. The use of the drug has been found to help in speedy recovery of hospitalized patients by reducing dependence on supplemental oxygen.

2-DG is powdered drug formulation and is taken by patient orally by dissolving it in water. It accumulates in the human body in virus-infected cells and prevents virus growth by stopping glycolysis and production of ATP for survival of virus cell.

India is in midst of a vicious second wave of covid-19 infections, and a large number of patients are needing hospitalization with supplemental oxygen support. The drug is to be considered as to save lives. This will also reduce the hospitalization of covid-19 infected persons.

On treatment with 2-DG higher proportion of patients showed RT-PCR test negative. The drug is to be of immensely beneficial to the people suffering from covid-19,

Tremendous faster symptomatic cure observed when the patients treated with 2-DG than that of Standard of Care (SOC). Median time to achieving normalization of specific vital signs parameters was found to be 2.5 days less as compared with SOC (Figure 7)

Figure 7: Effect of 2-DG administration

Antiviral activities of sugar derivatives have been reported by many investigators. Evidence indicated that 2-dG inhibited the multiplication of several enveloped viruses by interfering with the process of virus glycosylation as an anti-metabolite of mannose rather than glucose.

CONCLUSION

The 2-DG drug accumulates in the virus-infected cells and prevents virus growth by stopping viral synthesis, glycolysis and ATP production. The use of 2-DG drug has been found to help in faster recovery of moderate and serious patients, and in reducing supplemental oxygen dependence.

The new anti-Covid-19 oral drug developed by the DRDO will help hospitalized patients and reduce their supplemental oxygen dependence. The drug 2-DG has been developed by Defence Research and Development Organization (DRDO), in collaboration with Dr Reddy's Laboratories (DRL) in Hyderabad. 2-DG is powdered formulation in the form of sachet and advised to taken orally by dissolving it in water. Drugs Controller General of India (DCGI)

approved 2-dG for emergency use as an adjunct therapy.

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