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Research Article

GLUCOSE METABOLISM OF GINGIVA – A REVIEW

M.M. Dayakar., Mohamed Abdul Haleem*., Shivanand H and Abdul Waheed

Department of Periodontology, KVG Dental College and Hospital, Sullia D.K

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A B S T R A C T

Hundreds of reactions simultaneously take place in a living cell, in a well-organized and integrated manner. The entire spectrum of chemical reactions, occurring in the living system are collectively referred to as metabolism. Carbohydrate metabolism is a fundamental biochemical process that ensures a constant supply of energy to living cells. The most important carbohydrate is glucose, which can be broken down via glycolysis, enter into the Kreb's cycle and oxidative phosphorylation to generate ATP. A metabolic pathway constitutes a series of enzymatic reactions to produce specific products. As such, the metabolic pathways occur in specific locations (mitochondria, microsomes etc.) and are controlled by different regulatory signals. Cytoplasmic organelle concentration varies among different epithelial strata. Mitochondria are more numerous in deeper strata and decrease toward the surface of the cell.

Glycogen can accumulate intracellularly when it is not completely degraded by any of the glycolytic pathways. Thus, its concentration in normal gingiva is inversely related to the degree of keratinization and inflammation. The hexose monophosphate-shunt mechanism, the Embden-Meyerhof glycolysis scheme, citric acid cycle, mitochondrial terminal electron transport, and oxidative phosphorylation have been identified in gingiva and their relative activities are given in the above order. Glucose metabolism is impaired in uncontrolled diabetes in human oral mucosa. The neutrophil function may be impaired due to reduced glucose-6-phosphate dehydrogenase (G6PDH) activity. Neutrophils kills bacteria by building an oxidative burst. The respiratory burst requires the formation of NADPH. In neutrophils, pentose phosphate pathway is responsible for the formation of NADPH and ribose-5-phosphate for fatty acid and nucleotide synthesis, respectively.

INTRODUCTION

Hundreds of reactions simultaneously take place in a living cell, in a well-organized and integrated manner. The entire spectrum of chemical reactions, occurring in the living system are collectively referred to as metabolism.[1]

Carbohydrate metabolism is a fundamental biochemical process that ensures a constant supply of energy to living cells. The most important carbohydrate is glucose, which can be broken down via glycolysis, enter into the Kreb's cycle and oxidative phosphorylation to generate ATP.

Further important pathways in carbohydrate metabolism include the pentose phosphate pathway (conversion of hexose sugars into pentoses), glycogenesis (conversion of excess glucose into glycogen, stimulated by insulin), glycogenolysis (conversion of glycogen polymers into glucose, stimulated by glucagon) and gluconeogenesis (de novo glucose synthesis).

Corresponding author:* **Mohamed Abdul Haleem
Department of Periodontology, KVG Dental College and Hospital, Sullia D.K

A metabolic pathway constitutes a series of enzymatic reactions to produce specific products. [1]As such, the metabolic pathways occur in specific locations (mitochondria, microsomes etc.) and are controlled by different regulatory signals. For example, the enzymes of glycolysis pathway are present in the cytosomal fraction of the cell. The end product 'pyruvate' is converted to acetyl CoA by oxidative decarboxylation which continues to enter TCA cycle for further energy production. This reaction is catalyzed by a multienzyme complex, known as pyruvate dehydrogenase complex which is found only in the mitochondria.

Hexose monophosphate pathway or HMP shunt is also called pentose phosphate pathway, phosphogluconate pathway or direct oxidative pathwayis an alternative pathway to glycolysis and TCA cycle for the oxidation of glucose. The enzymes of HMP shunt are located in cytosol.[2]

Cellular contentswithin a cell keeps changing according to its degree and stage of keratinization. A complete keratinization process leads to the production of an orthokeratinized superficial horny layer similar to that of the skin, with no nuclei in the stratum corneum and a well-defined stratum

granulosum. Only some areas of the outer gingival epithelium are orthokeratinized; the other gingival areas are covered by parakeratinized or nonkeratinized epithelium, considered to be at intermediate stage of keratinization.[3]

Cytoplasmic organelle concentration varies among different epithelial strata. Mitochondria are more numerous in deeper strata and decrease toward the surface of the cell, accordingly; the histochemical demonstration of succinic dehydrogenase, nicotinamide adenine dinucleotide, cytochrome oxidase, and other mitochondrial enzymes reveals a more active tricarboxylic cycle in basal and parabasal cells, in which the proximity of the blood supply facilitates energy production through aerobic glycolysis.Conversely, enzymes of the pentose shunt (an alternative pathway of glycolysis), such as glucose-6-phosphatase increase their activity toward the surface. This pathway produces a larger amount of intermediate products for the production of ribonucleic acid (RNA), which in turn can be used for the synthesis of keratinization proteins. This histochemical pattern is in accordance with the increased volume and the amount of tonofilaments observed in cells reaching the surface; the intensity of the activity is proportional to the degree of differentiation.[4,5,6,7]

Glycogen can accumulate intracellularly when it is not completely degraded by any of the glycolytic pathways. Thus, its concentration in normal gingiva is inversely related to the degree of keratinization[8,9] and inflammation.[10,11,12]

Heavy deposits of glycogen are present in the keratinized marginal epithelium of inflamed human gingival tissue but not in the adjacent nonkeratinized crevicular epithelium that lines the gingival pocket. In normal gingivae the marginal epithelium was keratinized and free from glycogen deposits. In the inflamed gingivae, where leucocytic infiltration of only the connective tissue occurred, glycogen depositsare seen in the superficial cells of the marginal epithelium where the ribonucleic acid (R.N.A.) content was low, irrespective of the state of keratinization of the epithelium. Glycogen was not deposited in those portions of the marginal or crevicular epithelium where leucocytic infiltration extended from the connective tissue into the epithelium; R.N.A. content was low in these areas.[13]

The nonoccurrence of deposits of glycogen in the inflamed nonkeratinized crevicular epithelium may be explained by infiltration of this tissue by leucocytes and other elements; leucocytes possess both amylase and nuclease. It is known that some intercellular substance are lost during gingival inflammation, so that enzymes could more readily diffuse into the epithelium either from the gingival pocket or from the inflamed subepithelial zone and also glucose could more readily diffuse out of the epithelium.[13]

It is suggested, therefore, that the reason for glycogen deposition in inflamed gingiva is the presence of excess glucose (from gluconeogenesis) that diffuses into the epithelium. The glycogen that is deposited is apparently from glucose in excess of that which might be needed for keratinization and other syntheses and appears to be a mechanism for disposal of unwanted glucose.[13]

The hexose monophosphate-shunt mechanism, the Embden-Meyerhof glycolysis scheme, citric acid cycle, mitochondrial terminal electrontransport and oxidative phosphorylation have been identified in gingiva and their relative activities are given in the above order.[14]

Schrader *et al*. (1957) using manometric techniques studied aerobic glycolysis in human gingiva. He reported that addition of glucose as substrate did not alter the rate of endogenous respiration. The value of oxygen uptake of normal gingiva was found to be 1.77, as compared with 4.50, 2.69, and 3.19 observed respectively in slight, moderate and severe gingival inflammations. Respiratory quotient values observed for normal and slightly inflamed tissue were about 1.0, as compared to 1.67 and 2.45 observed in moderately and severely inflamed tissues. These data were considered to reflect a shift towards aerobic glycolysis as the degree of inflammation increased. Thus, he concluded that endogenous oxygen utilization by gingiva increases during mild to moderate inflammatory changes but declines as the inflammatory changes become more severe. There is also a concomitant decrease in the utilization of a variety of metabolic substrates as the severity of inflammation of the gingival tissue increases. The increase in on utilization in mild to moderate inflammation of gingiva may be in part due to the higher content of polymorphonuclearleukocytes in such tissue.[15]

Simpson (1974), he concluded that Embden-Meyerhof glycolysis in rat gingiva was slightly greater than that observed for the pentose-phosphate shunt in rat and canine gingiva. Also, rat gingival conversion of pyruvate to lactate was greater than pyruvate oxidation through pyruvate oxidase.[16] Hexokinase and 6-pbospliofruetokinase activities were reported to be particularly low in rabbit gingiva (Suzuki *et al*. 1982), This suggests that the above enzymes may play a vital or rate limiting role in modulating glycolysis in oral mucosa.[17]

Bergquist andNuki (1973) studied hexokinase and fructoaldolase activities in the variousepithelial layers of attached gingiva ofrhesus monkeys. Hexokinase activities were similar at the surface, granular and spinouslayers; and lower activities were detected inbasal and connective tissue layers. Fructoaldolase activities were similar in granularand basal layers, and progressively declined from the granular layer toward superficiallayers. Lower levels of activity were found inthe connective tissue.[18]

Nicolau *et al*. (1977) repotted that human attached gingiva has significantly greater phosphofructokinase, Hexokinaseand pyruvate kinase activities.[19]

There are significant differences in oxidative metabolism between inflamed and non-inflamed gingival tissues.The decline in O_2 utilization and oxidative metabolism in severely inflamed gingival tissue may be the result of tissue injury and destruction brought about by chronic polymorphonuclear leukocytes and other white cell populations.[20,21,22,23]

Lactic dehydrogenase activity was found to be relatively high in human, guinea-pig and rat gingiva suggesting that gingiva has a high glycolytic potential (Eichel & Shahrik - l964). [24] Charreau *et al*. (1966) reported that there was no significant difference in LDH activity between gingiva removed from the incisor and the molar regions.[25] Honjo *et al*. (1965) and Charreau *et al*. (1966) found liver LDH to be 2 and 4times more active, respectively than gingivalLDH.[26] The enzyme was also found to be twice as active in pathological human

gingiva as incontrol gingiva (Takiguchi *et al*. 1966).[27] Alvarez*et al*. (1972) found that LDH activity was 73% higher in hyperorthokeratinized andhyperparakeratinized epithelia of leukoplakiasthan in normal gingiva of humans.[28]

In human periodontitisTakiguchi-1966 found that the levels of isoenzymes 1, 2 and 5 were similar to those observed under normal conditions. However, twofold increases in LDH-3 and LDH-4 levels were observed in the pathological tissue. The presence of a relatively active LDH in gingiva also suggests that lactate might be degraded via the Krebs cycle in gingival metabolism.[29]

The distribution of glucose-6 phosphate dehydrogenaseand of succinic dehydrogenase invarious epithelial cell layers, and in connective tissue were evaluated in human andrabbit gingiva by Itoiz *et al*. (1972). In attachedand marginal gingiva, glueose-6-pliospliate dehydrogenase activity increased progressively from the basal cell layer to thesuperficial layer. This enzymatic activity remained stable in all strata of oral mucosal epithelium and crevicular epithelium but declined towards the surface of the epithelial attachment. In contrast, succinicdehydrogenase activity progressively declined from the basal cell layer towards the surface. These data suggested to both Simpson (1970)and Itoiz *et al*. (1972) that the pentose-phosphateshunt may be associated with gingival keratinization, as originally proposed byEichel and Shahrik (1964).[30]

While both the pentose-phosphate shuntand the Embden-Meyerhof pathways forglucose metabolism are present in gingiva, their relative contributions remain some what problematical. Both Schrader *et al*. (1959) and Simpson (1970) felt that the major pathwayis via the pentose-phosphate pathway. However, a later report by Simpson (1974) reversed this interpretation in favor of the Embden-Meyerhof scheme.[14]

Vitamin deficiencies (vitamin C, CoQ10 Ubiquinone) depress oxidative metabolismand electron transport mechanisms in human and animal gingiva.[31,32,33]

Glucose metabolism is impaired in uncontrolled diabetes in human oral mucosa. The neutrophil function may be impaired due to reduced glucose-6-phosphate dehydrogenase (G6PDH) activity. This is a rate-limiting enzyme in the pentose phosphate pathway. The neutrophils, macrophages, and lymphocytes isolated from diabetic rats have demonstrated a considerably decreased G6PDH activity.[34,35] Thus, in diabetics, pentose phosphate pathway is downregulated, which is required for the normal functioning of neutrophils. So, it has been proposed that decreased neutrophilic G6PDH activity in diabetic patients results in the impaired phagocytotic activity of neutrophils, impaired superoxide production and their reduced bactericidal activity.[36,37]

Neutrophils kills bacteria by building an oxidative burst. The respiratory burst requires the formation of NADPH. In neutrophils, pentose phosphate pathway is responsible for the formation of NADPH and ribose-5-phosphate for fatty acid and nucleotide synthesis, respectively.[38] NADPH is important for NADPH oxidase and glutathione activity in neutrophils.[39,40] In diabetic patients, NADPH production is decreased, which leads eventually to compromised neutrophil function. The lowering of blood glucose levels by insulin treatment has been reported to have a significant correlation with the improvement of phagocytosis capacity by neutrophils.[41,42]

It is suggested that quantitative studies of interrelationships between glucose metabolism and periodontal associational studies should be further studied in depth and that they will further increase our understanding of gingival and other periodontal tissues in health and disease.

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