International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 02 Issue 06 June 2022

Page No: 469-472

DOI: https://doi.org/10.47191/ijmscrs/v2-i6-05, Impact Factor: 5.365

Impact of Metformin on the Warburg Effect on Cancer Cells

José Maria Zepeda Torres[1], Héctor Zúñiga Gazcón[2], Carolina Covarrubias Castellón[2], Xchel Iván Campuzano Rodríguez[3], Félix Osuna Gutiérrez[1], Luis Adrián Flores Chávez[1], Carlos Arturo López Romero[1], Omar De Jesús Dorantes Rodríguez[4], Grecia Jazmin García Gutiérrez[5], Miriam Chantal Pérez Díaz [5], Saulo Gómez de Alba[1], Leonardo Ramírez Nucamendi[1]

[1]School of Medicine, Universidad Autónoma de Guadalajara, Guadalajara, Jalisco, Mexico.
[2]School of Medicine, Universidad Autónoma de Nayarit, Tepic, Nayarit, Mexico.
[3]School of Medicine, Universidad LAMAR, Guadalajara, Jalisco, Mexico.
[4]School of Medicine, Autonomous University of Querétaro, Querétaro, Querétaro, Mexico
[5]School of Medicine, University of Guadalajara, Guadalajara, Jalisco, México

ABSTRACT

It is complex to understand all the mechanisms by which tumor cells use for their survival. The aim of the present review is to propose the mechanisms by which metformin would be beneficial in the context of cancer through the inhibition of the Warburg effect. A literature review of the Warburg effect and the mechanism of action of metformin was carried out to determine a theoretical relationship betweenmetformin consumption and inhibition of tumor cell metabolism. There are several mechanisms through which metformin could antagonize tumor cells. As authors, weconsider it of vital importance to know these effects in order to extrapolate them to experimental studies and seek the maximum benefit for patients, using the resourceswe have to date.

ARTICLE DETAILS

Published On:
08 June 2022

Available on:
https://ijmscr.org/

INTRODUCTION

It is complex to understand all the mechanisms by which tumor cells use for their survival. Initially, there is uncontrolled proliferation and the acquisition of genetic alterations that allow them to grow outside the primary site, giving them adaptive advantages over healthy cells[1].

During the 1920s, Otto Warburg and his colleagues observed that tumors utilized large amounts of glucose relative to the surrounding tissue, noting that the rate of fermentative glycolysis increased even under aerobic conditions. It is known that fermentation is independent of oxygen, so Warburg's phenomenon was a contradiction to the Pasteur effect[1, 2].

Metformin is an oral antidiabetic belonging to the biguanides, it decreases hyperglycemia through hepatic suppression of glucose production. In addition, it increases insulin sensitivity, enhances peripheral glucose uptake (by inducing phosphorylation of GLUT4-enhancing factor), decreases insulin-induced suppression of fatty acid oxidation, and decreases glucose absorption from the gastrointestinal tract[3]. However, the underlying molecular mechanism is only partially understood. Inhibition of the mitochondrial respiratory chain, activation of AMP-activated protein kinase, inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP), consequent activation of protein kinase A(PKA), inhibition of mitochondrial glycerophosphate dehydrogenase, and an effect on the gut microbiota have been proposed as potential mechanisms[4-6] .

The aim of the present review is to propose the mechanisms by which metformin would be beneficial in the context of cancer through the inhibition of the Warburg effect.

METHODS

A literature review on the Warburg effect and the mechanism of action of metforminwas carried out to determine a theoretical relationship between metformin consumption and the inhibition of tumor cell metabolism; for this purpose, a search was carried out in several databases, preferably using those published 5 years ago,although some older ones were included since their relevance is justified.

THEORETICAL FRAMEWORK

Metabolism of healthy cells

Under normal circumstances the cell produces ATP to meet its needs by coupling two catabolic mechanisms; firstly, glycolysis, which consists of 10 enzymatic reactions responsible for degrading glucose to pyruvate, and secondly, the Krebs cycle, which provides greater energy efficiency during the complete oxidation of glucose due to the presence of oxygen. Pyruvate is condensed within the mitochondria by coenzyme A and oxaloacetate. Complete oxidation of pyruvate continues through the tricarboxylic acid cycle, the respiratory chain and oxidative phosphorylation. Due to both mechanisms approximately 90% of the energy required for normal cell function is obtained[1, 7].

Metabolism in the context of cancer

At the cellular level tumors present evolutionary advantages for lactate secretion[8]. The expression and coupling of vascular endothelial growth factor and its receptor respond to different stimuli for angiogenesis, among these stimuli is the increased expression of hypoxia inducible factor 1, which in turn is positively stimulated by theacidic and anaerobic environment. Other stimuli involved include activation ofoncogenes such as RAS, MYC, AKT and mutation of tumor suppressor genes such as p53. Stimulation of VEGF and its receptor are intended to generate greater oxygenation to the cells to promote oxidative metabolism and suppress fermentative glycolysis, however, paradoxically, metastasis is promoted[9].

Under oxygen limitation pyruvate is reduced to lactate. If there are failures in the respiratory chain the oxidation of NADH+H+ does not occur by this pathway.Because of this, the transition from pyruvate to lactate is a critical point in the metabolism of tumor cells[10]. In tumor cells, changes in the expression of lactate dehydrogenase enzyme isoforms have been demonstrated and it was observed thattumor cells deficient in lactate dehydrogenase showed increased mitochondrial respiration[11]. The acidic environment is hostile and normal cells die due to lack of cellular mechanisms to adapt to the extracellular acidity[12, 13]. This promotes the adaptation of the fittest cells that resist an acidic environment in the context of rapid proliferation, in turn preventing the mounting of an immune response against it and thus facilitating selection mechanisms for uncontrolled growth of tumor tissue[14].

Direct and indirect antitumor mechanisms of metformin

The mechanism of action of metformin involves negative regulation of the insulin/insulin-like growth factor axis, a mechanism that has been demonstrated in patients with type 2 diabetes mellitus and women with polycystic ovary syndrome[15-17] . Current observations have focused on the ability of this drug to activate AMPK through the tumor suppressor LKB1, a tumor suppressor kinase whose inactivationleads to Peutz-Jeghers syndrome[18, 19] . Activation of AMPK, results in a positive regulation of oxidative metabolism and reduced anabolism[20] . In addition to direct phosphorylation effects on key metabolic targets such as acetyl CoA and phosphofructokinase 2, AMPK activation also leads to mTOR inhibition that decreases signaling through Akt kinase and decreases the efficiency of protein synthesis through decreased phosphorylation of mTOR targets 4EBP-1 and S6K[21-24] . Cap-dependent inhibition of translation in response to metformin can decrease the expression of Her2 , an oncogene and cyclin D1[25-27] .

Finally, AMPK-independent antitumor effects of metformin action have been demonstrated, such as inhibition of Rag GTPase-dependent mTOR and growth inhibition of AMPK-silenced ovarian cancer cells[28]. Researchers described that metformin could inhibit mitochondrial oxidation of complex I-dependent substrates inhepatocytes, and this effect extrapolates to isolated mitochondria[29]. This inhibition of complex I may contribute to AMPK activation due to decreased oxidative phosphorylation capacity and a consequent decrease in the ATP/AMP ratio, a phenomenon that explains the lactic acidosis observed in response to high doses ofmetformin[30].

DISCUSSION

It has been consistently shown that inhibition of hepatic gluconeogenesis is an AMPK-independent consequence of decreased intracellular ATP levels, a fact that suggests that the pleiotropic effects of this agent could be the result of a targeted effect on the mitochondrial electron transport chain[31]. This effect is more intriguing in light of recent observations demonstrating that inhibition of electron transport in cancer cells is fatal to cancer cells[32-34], because the accumulation of NADH in the mitochondrial matrix inhibits the Krebs cycle and its associated anaplerotic reactions that sustain biomass generation[35]. Furthermore, it is suggested that electron transport, uncoupled from oxidative phosphorylation, antagonizes the initiation of apoptosis in tumor cells[35, 36] , supporting the hypothesis that the chemotherapeutic effects of

metformin may result from its ability to inhibit the mitochondrial complex.

The authors of this literature review considered this topic in order to establish a causal relationship between these effects of metformin and the mechanisms of cancer. It is thanks to the arguments reflected in the preceding paragraphs that we justify the need for this paper.

Now, with regard to the bibliography we have selected for this work, we were able toreach the conclusion that it is refined, since the articles and books that compose it have followed international parameters to be valid, a reflection of this is that they appear in scientific journals or belong to prestigious publishers, as the case may be.In addition, they are conclusive in their results.

In the strict sense of the word, we are aware that this cannot be a discussion, sincethe central thesis of the present work has not been to confront information, but ratherto try to enunciate the molecular mechanisms by which metformin would be beneficial in selected types of cancer.

CONCLUSION

As authors, we consider it vitally important to know these effects in order toextrapolate them to experimental studies and seek the maximum benefit for patients,using the resources we have to date.

REFERENCES

I. Herrera-González, N. E., Martínez-García, F., & Mejía-Jiménez, E. (2015). The Warburg effect: the right hand in cancer development. Journal of Medical- Surgical Specialties, 20(2), 171-177.

II. Liberti, M. V., & Locasale, J. W. (2016). The Warburg effect: how does it benefit cancer cells?. Trends in biochemical sciences, 41(3), 211-218.

III. 3. Jia, Y., Ma, Z., Liu, X., Zhou, W., He, S., Xu, X., ... & Tian, K. (2015).

IV. Metformin prevents DMH-induced colorectal cancer in diabetic rats by reversing the warburg effect. Cancer medicine, 4(11), 1730-1741.

V. Rena, G., E. R. Pearson, and K. Sakamoto. 2013. Molecular mechanism of action of metformin: old or new insights? Diabetologia 56:1898-1906.

VI. Burcelin, R. 2014. The antidiabetic gutsy role of metformin uncovered? Gut 63:706-707.

VII. Madiraju, A. K., D. M. Erion, Y. Rahimi, X.-M. Zhang, D. T. Braddock, R. A. Albright, et al. 2014. Metformin suppresses gluconeogenesis by inhibiting mitochondrial glycerophosphate dehydrogenase. Nature 510:542-546.

VIII. Casado Pinna M. (2009). Regulation of gene expression by glucose. Monographs of the Royal National Academy of Pharmacy.

IX. Archetti, M. (2014). Evolutionary dynamics of the Warburg effect: Glycolysis as a collective action problem among cancer cells. Journal of theoretical biology, 341,1-8.

X. Martínez-Ezquerro, J. D., & Herrera, L. A. Angiogenesis: VEGF/VEGFRs as Therapeutic Targets in Cancer Treatment. Instituto Nacional de Cancerología-Instituto de Investigaciones Biomédicas, 83-88.

XI. Marín, A.H (2009). Hypoxia-induced factor-(HIF-1) and glycolysis in tumor cells. Journal of Biochemical Education, 28(2),42-51.

XII. Gonzalez Rengifo, G. F., Gonzales Castañeda, C., Espinosa Guerinoni, D., & Rojas Tubeh, C. (2007). Overexpression of glycolytic pathway enzyme genes in cancer cells. Acta Médica Peruana, 24(3),187-197.

XIII. Archetti, M. (2014). Evolutionary dynamics of the Warburg effect: Glycolysis as a collective action problem among cancer cells. Journal of theoretical biology, 341,1-8.

XIV. Nijsten, M. W., & van Dam, G. M. (2009). Hypothesis: using the Warburg effect against cancer by reducing glucose and providing lactate. Medical hypotheses, 73(1),48-51.

XV. Thorne, J. L., & Campbell, M. J. (2014). Nuclear receptors and the Warburg effect in cancer. International Journal of Cancer.

XVI. Anisimov VN, Berstein LM, Egormin PA, Piskunova TS, Popovich IG, Zabezhinski MA, Kovalenko IG, Poroshina TE, Semenchenko AV, Provinciali M, Re F, Franceschi C. Effect of metformin on lifespan and development of spontaneous mammary tumors in HER-2/neu transgenic mice. Experimental Gerontology 2005;40:685-693.

XVII. Wysocki PJ, Wierusz-Wysocka B. Obesity, hyperinsulinemia, and breast cancer: new targets and a new role for metformin. Expert Reviews of Molecular Diagnostics 2010;10:509-519.

XVIII. Motta AB. Mechanisms involved in the action of metformin in the treatment of polycystic ovary syndrome. Current Pharmaceutical Design 2009;15:3074- 3077.

XIX. Shaw RJ, Lamia KA, Vasquez D, Koo SH, Bardeesy N, Depinho RA, Montminy M, Cantley LC. LKB1 kinase mediates liver glucose homeostasis and the therapeutic effects of metformin. Science 2005;310: 1642-1646.

XX. Huang SC, Erdman SH. Pediatric juvenile

polyposis syndromes: an update. Current gastroenterology report 2009;11:211-219.

XXI. Luo Z, Zang M, Guo W. AMPK as a metabolic tumor suppressor: control of metabolism and cell growth. Future Oncology 2010;6:457-470.

XXII. Cao C, Lu S, Kivlin R, Wallin B, Card E, Bagdasarian A, Tamakloe T, Wang WJ, Song X, Chu WM, Kouttab N, Xu A, Wan Y. SIRT1 confers protection against UVBand H2O2-induced cell death through modulation of p53 and JNK in cultured skin keratinocytes. Journal of Cellular and Molecular Medicine 2009;13:3632-3643.

XXIII. Kimura N, Tokunaga C, Dalal S, Richardson C, Yoshino K, Hara K, Kemp BE, Witters LA, Mimura O and Yonezawa K. A possible link between AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR) signaling pathway. Genes to Cells 2003;8:65-79.

XXIV. Zakikhani M, Blouin MJ, Piura E, Pollak MN. Metformin and rapamycin have distinct effects on the AKT pathway and proliferation in breast cancer cells. Breast Cancer Research and Treatment 2010. - epub ahead of print. paper reference not ready.

XXV. Han S, Khuri FR, Roman J. Fibronectin stimulates non-small cell lung carcinoma cell growth through activation of Akt/mammalian target of rapamycin/S6 kinase and inactivation of LKB1/AMP-activated protein kinase- activated protein kinase signaling pathways. Cancer Research 2006;66:315- 323.

XXVI. Dowling RJ, Zakikhani M, Fantus IG, Pollak M, Sonenberg N. Metformin inhibits the mammalian target of rapamycin-dependent translation initiation in breast cancer cells. Cancer Research 2007;67:10804-10812.

XXVII. Vázquez-Martin A, Oliveras-Ferraros C, Menendez JA. The antidiabetic drug metformin suppresses HER2 (erbB-2) oncoprotein overexpression through inhibition of the mTOR effector p70S6K1 in human breast carcinoma cells. Cell Cycle 2009;8:88-96.

XXVIII. Ben S, I, Laurent K, Loubat A, Giorgetti-Peraldi S, Colosetti P, Auberger P, Tanti JF, Le Marchand-Brustel Y, Bost F. The antidiabetic drug metformin exerts an antitumor effect in vitro and in vivo through a decrease in cyclin D1 level. Oncogen 2008;27:3576-3586.

XXIX. Kalender A, Selvaraj A, Kim SY, Gulati P, Brule S, Viollet B, Kemp BE, Bardeesy N, Dennis P, Schlager JJ, Marette A, Kozma SC, and Thomas G. AMPK-independent metformin inhibits mTORC1 in a GTPase-dependent manner. Cell Metabolism 2010; 11:390-401.

XXX. Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its antidiabetic effects through inhibition of mitochondrial respiratory chain complex 1. Biochemical Journal 2000;348 Pt 3:607-614.

XXXI. Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Systems Review 2010;4:CD002967.

XXXII. Foretz M, Hebrard S, Leclerc J, Zarrinpashneh E, Soty M, Mithieux G, Sakamoto K, Andreelli F, Viollet B. Metformin inhibits hepatic gluconeogenesis in mice independently of the LKB1/AMPK pathway through a decrease in hepatic energy status. Journal of Clinical Investigation 2010;120:2355-2369.

XXXIII. Samudio I, Kurinna S, Ruvolo P, Korchin B, Kantarjian H, Beran M, Dunner K Jr, Kondo S, Andreeff M, Konopleva M. Inhibition of mitochondrial metabolism by methyl-2-cyano-3,12-dioxooleana-1,9-diene-28-oate induces apoptotic or autophagic cell death in chronic myeloid leukemia cells. Molecular Cancer Therapeutics 2008;7:1130-1139.

XXXIV. Samudio I, Harmancey R, Fiegl M, Kantarjian H, Konopleva M, Korchin B, Kaluarachchi K, Bornmann W, Duvvuri S, Taegtmeyer H, Andreeff M. Pharmacological inhibition of fatty acid oxidation sensitizes human leukemic cells to induction of apoptosis. Journal of Clinical Investigation 2010;120:142- 156.

XXXV. Samudio I, Konopleva M, Pelicano H, Huang P, Frolova O, Bornmann W, Ying Y, Evans R, Contractor R, Andreeff M. A novel mechanism of action of methyl- 2-cyano-3,12 dioxoolean-1 ,9 diene-28-oate (CDDO-Me): direct permeabilization of the inner mitochondrial membrane to inhibit electron transport and induce apoptosis. Molecular Pharmacology 2006;69:1182- 1193.

XXXVI. Samudio I, Fiegl M, Andreeff M. Mitochondrial uncoupling and Warburg effect: molecular basis for reprogramming cancer cell metabolism. Cancer Research 2009;69:2163-2166.

XXXVII. Samudio I, Fiegl M, McQueen T, Clise-Dwyer K, Andreeff M. The Warburg effect in leukemia-estroma cocultures is mediated by mitochondrial uncoupling associated with activation of uncoupling protein 2. Cancer Research 2008;68:5198-5205.