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NARRATIVE REVIEW

Hyperwarburgism: the "happy hypoglycemia" of cancer patients: Narrative review

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Abstract

Introduction: Glucose is the cerebral energy fuel; this relationship is fully established in most reviews due to neuronal tissue's avid and almost exclusive glucose consumption. In this sphere, hypoglycemia is translated by default into a set of neurological symptoms resulting from the neuroglycopenic state. When the drop in these glycemic levels is pronounced, it triggers alterations in the sensory state, being able to reach a coma with irreversible damage if sustained over time.

Purpose of the review: The objective is to present a case of severe hypoglycemia without neuroglycopenic symptoms.

Recent findings: The absence of neurological symptoms is due to the consumption of lactate – traditionally an anaerobic product – as an alternative energy metabolic pathway to glucose consumption. Hypoglycemia can be compensated at the neurological level with lactate launching systems in neuronal tissue, replacing glucose as the brain's energy substrate.

Conclusions: Hypoglycemia without adrenergic or neuroglycopenic symptoms is an issue linked to cancer patients, and lactate is proposed as fuel for nervous tissue in addition to glucose. On the other hand, the lactate-hypoperfusion association is another entity that must be reviewed and reanalyzed for everything that lactate implies within the body's metabolic pathophysiological pathway.

Keywords:
MESH: Hypoglycemia, Lactic acid, Pyruvic acid, Medical oncology, Anaerobiosis, Metabolic encephalopathy.

Introduction

The complexity of the known metabolic pathways can only be overshadowed by the number of alternatives to traditional pathways that could be developed at the cellular level, many of

which have been studied and others whose physiological or pathophysiological explanation is not well known.

Within this context, the oncology section deserves particular mention. Neoplastic cells are characterized by a unique metabolism, developed with specific characteristics to replace the high energy demand necessary for excessive proliferation. The goal of the tumor is to divide and grow; for this to happen, it must be in a hypoxic environment [1] and with a high lactate concentration [2].

Each tumor to fulfill its pathological proliferation is governed by a phenomenon described in 1920 by Otto Warburg called the "Warburg effect" [3]. This effect is shown as an alteration of the normal metabolism of glucose due to the exaggerated increase in its consumption by neoplastic cells. However, unlike normal cells, cancer cells take an alternative route to produce energy; glucose, instead of being transported to the mitochondria, is transported to the cytoplasm, where lactate is transformed into pyruvate to access the tricarboxylic acid pathway (a process mediated through the enzyme lactate dehydrogenase) and is then secreted (aerobic glycolysis) [3].

Glycolysis causes a change in the tumor cell environment. Elevated lactate in the body acts as a cellular energy substrate, which protects against hypoglycemic events [4]. As the study of lactate progresses, this "Warburg effect" is not exclusive to cancer cells, as it can also occur in other tissues. The effect of not presenting adrenergic signs or symptoms or neuroglycopenia has been reported in cancer patients presenting episodes of hypoglycemia since lactate also feeds neuronal cells, a rare process described as hyperwarburgism [5]. Little literature on hyperwarburgism is described in the leading medical reference libraries, the vast majority of cancer patients (66% of cases).

Materials and methods

Study design

A search was performed in the United States National Library of Medicine (MEDLINE) database through The United States National Library of Medicine and National Institutes of Health (PUBMED) with the following search details:

- Date: between 1960 and 2021
- Languages: all those of the search engine
- Terms used: using the terms " hypoglycemia " + " warburg " + " effect ".

Nineteen articles were identified, including bibliographic reviews, analyses, and investigations, along with three review articles of 3 cases, 2 of which were linked to neoplastic processes and 1 in a nononcological patient. It is mentioned that other keywords were used without variability in the results obtained, and the search tree by MeSH terms had no different consequences.

Definitions

The precise definition of hypoglycemia is currently under debate; however, the American Diabetes Association (ADA) describes hypoglycemia as a clinical condition characterized by low blood glucose concentrations, usually less than 70 mg/dL (3.89 mmol/L) [6]. Diagnosis of hypoglycemia is based on Whipple's triad, which is described as low blood glucose, symptoms

of hypoglycemia, and symptom improvement once glycemia normalizes [7]. We can classify the symptoms of hypoglycemia as adrenergic (tachycardia, palpitations, tremors, sweating, paleness, and anxiety) and nonadrenergic or neuroglycopenic (hunger, headache, weakness, visual disturbances, confusion, lethargy, seizures, and even coma) [7]. A differential diagnosis would be considered (due to the presence of hypoglycemia without etiology) with insulinoma, which was not captured by the imaging studies carried out within its oncological analysis (paraclinical rule out) together with the absence of neuroglycopenic symptoms as cited (clinical rule out). Glucose is the primary substrate used by the brain. As such, multiple regulatory mechanisms exist to maintain blood glucose concentrations within normal parameters [8]; however, it is not the only substrate from which the brain can derive energy [9]. Showing lactate as a viable energy alternative. Experimental and clinical data provide many arguments in favor of this hypothesis, mainly suggesting that lactate is a possible and sometimes even mandatory substrate for the brain in an energy crisis [9]. Lactate, from 1780 and even up to recent years, was analyzed and described as the final waste product of metabolic pathways under anaerobic conditions with no other pathway than its subsequent clearance, formed in times of poor perfusion or hypoxia, an important marker of organ dysfunction [10], and its usefulness outside of being an indicator of the processes above of low perfusion and sepsis has been questioned for decades [11].

Lactate in the literature

Reviewing the literature on lactate, similar to other authors, we will first mention one of the body's energy deposit sites: skeletal muscle. We know that skeletal muscle is a storage fuel, being a reservoir of glycogen that can be broken down to lactate (not just glucose [12]) in response to the binding of β-adrenergic stimulants to the muscle cell membrane [12]. Lactate generated after beta-adrenergic stimulation is distributed passively down the concentration gradient out of the cell, passing into other tissues via monocarboxylate transporters (MCTs), where it can be used as fuel [4, 14]. In his research on lactate, Daniel specifies that this mechanism in traumatic situations, stress, or high energy requirements allows rapid fuel consumption at low cost [13]. Lactic acid dehydrogenase, or lactate dehydrogenase (LDH), is an essential enzyme of the anaerobic metabolic pathway that catalyzes the reaction of pyruvate to lactate [14]. Lactate dehydrogenase has higher activity than other enzymes in glycolysis or oxidative metabolism [14]. As a result of LDH activity, lactate is constantly formed and consumed almost instantaneously [15], which is why its serum levels under normal conditions are incipient (<2 mmol/L).

Astrocyte lactate transporter system (ANLS)

Since the body has a large deposit in glycogen, lactate, in particular situations, becomes an excellent source of fuel for most tissues, and the central nervous system, which our review includes, is no exception. Pellerin and Magistretti 1994 introduced the astrocyte-neuron lactate transporter (ANLS). This transporter system is proposed to molecularly explain the consumption of lactate instead of glucose in neuronal tissue. Under the premises of this system, astrocytes take up glucose (influenced by glutamate reuptake) and then release lactate for use by neurons attached to the system [15].

In ANLS, the astrocyte makes the energetic link between the capillary and the neuron through the intercellular lactate transport system. When electrical stimulation produces neuronal activation (neuronal membrane activity), large amounts of glutamate (among other neurotransmitters) are released into the synaptic cleft [16]. This glutamate neurotransmitter must be quickly reabsorbed to be transformed into glutamine, which requires energy. Glutamate reuptake in astrocytes triggers increased glucose uptake from capillaries (an energy-supplying molecule), a process regulated by isoform 2 of the Na+/K+-ATPase pump [17]. The generation of lactate provides the energy required by astrocytes for these processes (ATP) from actively captured capillary glucose (glycolysis), a process regulated by lactate dehydrogenase (LDH) isoenzyme 5 [18]. Lactate produced within the astrocyte must continue to the neuron. This lactate exchange is carried out by monocarboxylate transporters 1 and 4 (MCT1 and MCT4), which, according to the approach, are present in astrocytes [19]. Bittar et al., in their immunohistochemical and positron emission tomography (PET) studies, support the notion of a regulated lactate flow between astrocytes and neurons with the participation of the different LDH isoenzymes [20]. In this way, the lactate produced inside the astrocyte mediated by the LDH isoenzyme five will be recaptured by the neurons through monocarboxylate transporter 2 (MCT2), which is present in the neuron, to join the Krebs cycle prior to the action of LDH isoenzyme one that converts lactate into pyruvate, now as pyruvate to be part of the tricarboxylic acid pathway, resulting in obtaining energy for the maintenance of neuronal functions [20] and continuing synaptic transmission with the production of neurotransmitters glutamate, aspartate and gamma-aminobutyric acid (GABA) [17, 18, 19] glutamate that will return to the presynaptic space and will be reuptake by the astrocyte to repeat the cycle (Figure 1).

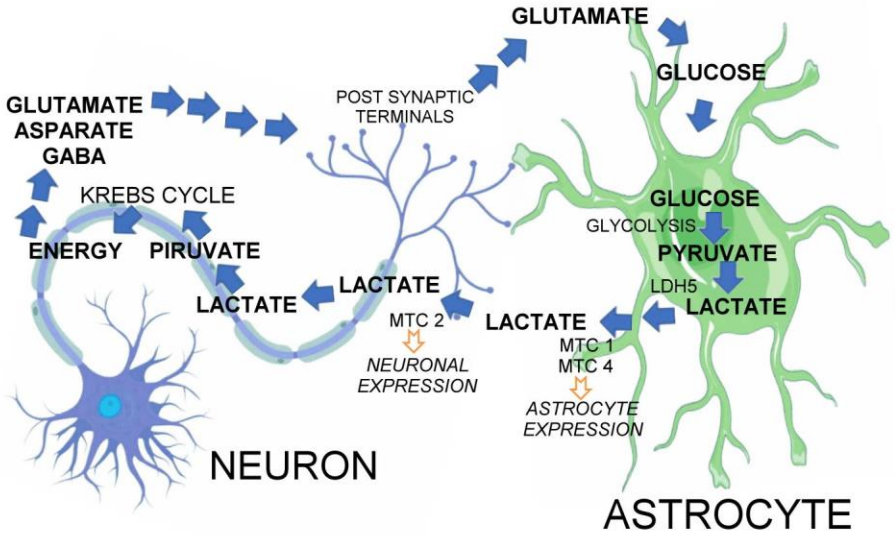

Figure 1. Schematic representation of proposed lactate transport between astrocytes and neurons (ANLS). (Pellerin and Magistretti, 1994, 1997 – Modified by authors). Capillary glucose performs via glycolysis the production of pyruvate, which, in the presence of high concentrations of LDH5 without the need for anaerobiosis, is transformed into lactate, which passes to the neuron via MCT 1 and 2 to return to its tricarboxylic form of pyruvate mediated by LDH1 and participate in the Krebs cycle.

MCT analysis

MCTs are a proper input/output system that allows molecular flow between plasma and neuronal tissue. That lactate is continuously formed and used under fully aerobic conditions has

been a proven truth for decades [12]. The discoveries of many lactate exchangers at the tissue level, including with different cell lines, have led to the articulation of numerous "lactate transporter systems" between producer and consumer cells [18]. The Pellerin/Magistretti model proposes MCT1 and MCT4 as those responsible for lactate export by astrocytes. In contrast, MCT2 has been proposed as a transporter that incorporates lactate into neurons [15, 19], leading to the flow of lactate between both cells for the final use of lactate in the Krebs cycle [20]. This proposed hypothesis fits with the operation of the ANLS system. However, Ferguson, in his study, considers that all MCTs are not unidirectional; that is, they allow the flow of the substrate in both directions [10]; studies on their distribution have shown that their expression is specific in certain tissues: MCT1 is expressed in astrocytes, oligodendrocytes, endothelial cells, and many other tissues throughout the body; MCT4 is expressed in astrocytes but not in neurons (as well as in muscle cells and some other places in the body); and MCT2 is found predominantly in neurons [15, 19]. Although the concept of ANLS and the experiments that support it have been debated, the importance of lactate within the central nervous system (CNS) is evident. It is a valid hypothesis to justify clinical processes in hypoglycemic/hyperlactatemia states.

Hyperwarburgism in the medical literature

Three reports of hyperwarburgism were found in the literature. The case presented by Elhosmy et al. corresponds to a 64-year-old woman who, despite presenting hypoglycemia, did not have any clinical manifestation of neuroglycopenia, despite serum glucose of 26 mg/dL (1.4 mmol/liter) and serum lactate of 28.5 mmol/L. The patient presented with an oncological diagnosis of diffuse large B-cell lymphoma. Despite the dextrose infusions, they reported no increase in blood glucose, but paradoxically, there was an increase in serum lactate. Goyal et al. presented the case of a 52-year-old man with severe but asymptomatic hypoglycemia in the oncologic setting of diffuse large B-cell lymphoma [21]. Loeb et al., however, presented a noncancer patient: an 85-year-old woman who presented with hyperwarburgism in the context of hemorrhagic shock with no cancer history [22].

Table 3. Hyperwarburgism in the medical literature.

Authors	Patient	Oncology	hypoglycemia	hyperlactatemia	neuroglycopenia
Elhosmy et al	female, 64a	Yes: Diffuse B-cell lymphoma	Yes	Yes	Nope
goyal et al	more, 52a	Yes: Diffuse B-cell lymphoma	Yes	Yes	Nope
Loeb et al	female, 85th	Nope	Yes	Yes	Nope

The ANLS system proposed by Pellerin and Magistretti satisfactorily provides the molecular explanation of the process: in states of hypoglycemia with decreased glucose supply to the neuronal tissue, this, via the neuronal astrocyte lactate transporter, takes up lactate produced in the astrocyte to maintain the energy supply of the neuron to continue its functions. This process is one of the many that continues to accumulate data in favor of lactate as the leading participant in metabolism and that neurons have alternative pathways to obtain their energy, not only in cancer patients (where there is more evidence) but also in noncancer patients where studies would be lacking to demonstrate the case of Loeb.

Conclusions

Hypoglycemia without adrenergic or neuroglycopenic symptoms is a rare topic in literature reviews. Widely linked to cancer patients but not exclusive to them, it is no longer a metabolic curiosity to become a valid topic of interest in neuronal metabolism since the sustained belief that glucose is the only fuel for tissue is in check highly strung. The analysis would remain to determine under what circumstances lactate comes into play through the ANLS to generate energy since there are cases in which it occurs outside the neoplastic environment. Knowing and elucidating the mechanisms that condition the use of alternative neural energy pathways would allow a better understanding of brain metabolism, which would open doors to search for protective therapies in cases of hypoperfusion or drop in energy intake for different reasons and would allow us to provide adequate support to care for the neural system. On the other hand, the lactate-hypoperfusion association is another entity that must be reviewed and reanalyzed for everything that lactate implies within the body's metabolic pathophysiological pathway.

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Administrative information

Abbreviations

ANLS: Neuronal astrocyte lactate transporter system.
MCT: monocarboxylate transporter.
CNS: central nervous system.

Additional Files

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Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

Author contributions

Fernando Roosemberg Ordoñez: Conceptualization, Formal analysis, Research, methodology, Project administration, Supervision, Validation, Visualization, Writing-original draft, Writing-revision, and editing.
José Veliz Ortega: Conceptualization, formal analysis, research, validation, writing-revision, and editing.
Valeria Ortega Uscocovich: Conceptualization, formal analysis, research, validation, writing-revision, and editing.
Aquiles Bowen Flores: Supervision, validation, writing-revision, and editing:
Carlos García Cruz: formal analysis, research, methodology, validation, visualization, writing -original draft.
All authors read and approved the final version of the manuscript.

Ethics committee approval

It does not apply to observational studies and narrative reviews.

Consent for publication

It does not apply when the patients' images, X-rays, or tomographies are not published.

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