Review

Bench-to-bedside review: A possible resolution of the glucose paradox of cerebral ischemia

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Abstract

The glucose paradox of cerebral ischemia (namely, the aggravation of delayed ischemic neuronal damage by preischemic hyperglycemia) has been promoted as proof that lactic acidosis is a detrimental factor in this brain disorder. Recent studies, both *in vitro* and *in vivo*, have demonstrated lactate as an excellent aerobic energy substrate in the brain, and possibly a crucial one immediately postischemia. Moreover, evidence has been presented that refutes the lactic acidosis hypothesis of cerebral ischemia and thus has questioned the traditional explanation given for the glucose paradox. An alternative explanation for the aggravating effect of preischemic hyperglycemia on the postischemic outcome has consequently been offered, according to which glucose loading induces a short-lived elevation in the release of glucocorticoids. When an episode of cerebral ischemia in the rat coincided with glucose-induced elevated levels of corticosterone (CT), the main rodent glucocorticoid, an aggravation of the ischemic outcome was observed. Both the blockade of CT elevation by chemical adrenalectomy with metyrapone or the blockade of CT receptors in the brain with mifepristone (RU486) negated the aggravating effect of preischemic hyperglycemia on the postischemic outcome.

Keywords cerebral ischemia, corticosterone, glucose, lactate, neuronal damage

The lactic acidosis hypothesis of cerebral ischemia [1–3] postulates that lactic acid accumulates in the brain during an ischemic event and plays a major detrimental role in delayed neuronal damage postischemia. The findings of Myers and Yamaguchi [4] that glucose administration preischemia significantly aggravates the postischemic outcome have been reproduced numerous times, and have repeatedly been promoted as the validation of the lactic acidosis hypothesis of cerebral ischemia.

The glucose paradox as proof of the validity of this hypothesis is based on the idea that preischemic hyperglycemia leads to elevated lactic acid levels, and thus to aggravation of postischemic brain damage. Preventive measures are consequently being practiced in hospitals throughout the world, including the close monitoring and tight control of blood glucose levels [5,6]. Nonetheless, such measures are in disagreement with several facts. First, glucose is the only major aerobic and anaerobic energy substrate in the brain. Second, during cerebral ischemia, glycolytic utilization of glucose is the only metabolic process capable of producing significant levels of ATP until all glucose and glycogen levels are extinguished. Third, during ischemia, lactate is the main product of glycolysis; on reperfusion/reoxygenation, when brain glucose is all but gone, the abundant lactate can easily enter the tricarboxylic acid cycle to maintain ATP production as efficiently as does glucose. Thus, paradoxically, the only process that supplies ATP to the ischemic tissue is viewed as the one responsible for the aggravation of the ischemic damage to this very tissue.

CT = corticosterone; RU486 = mifepristone.

Both *in vitro* studies [7–13] and *in vivo* studies [14–28] have shown that preischemic glucose supply is not necessarily harmful, and that it could even be beneficial when provided preischemia. These *in vivo* findings are considered oddities, however, while *in vitro* data are not considered to necessarily represent the true *in vivo* situation. Consequently, when dexamethasone treatment in stroke patients was found to induce hyperglycemia, Wass *et al*. [29] suggested that lactic acidosis, not the steroid itself, is responsible for the exacerbation of ischemic damage frequently observed with dexamethasone treatment. It is important to note, however, that steroids such as dexamethasone are regularly administered postischemia. Postischemic hyperglycemia has been shown not to aggravate postischemic damage [30–32]. In contrast, an association between a pronounced systemic stress response, an elevated level of cortisol in the plasma and increased mortality or morbidity has been reported [33].

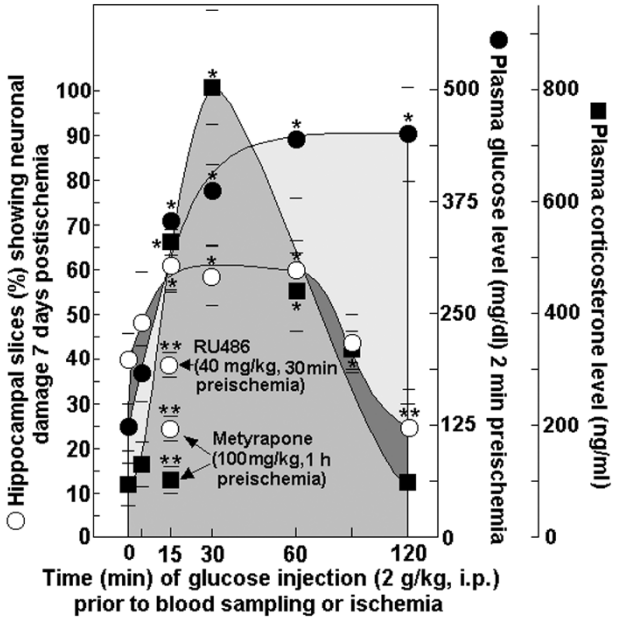
The steroid prednisone was shown to inhibit insulin secretion and to elevate blood glucose levels [34]. CT, the rodent equivalent of human cortisol, was shown to depress the release of glucose-induced insulin [35], while other studies have concluded that hyperglycemia in acute stroke patients represents a stress response [36,37]. Glucocorticoids have been shown to inhibit glucose transport and glutamate uptake in hippocampal astrocytes [38], to accelerate ATP loss following metabolic insults in neuronal culture [39], and thus to exacerbate insult-induced declines in energy metabolism [40]. A recent *in vitro* study was able to demonstrate an aggravation of ischemic damage by CT *in vitro* [41].

Until recently, no studies had been conducted to determine whether glucose loading preischemia induces an elevation in blood glucocorticoids (see below). In an unrelated study, Harris *et al*. [42] found that glucose challenge in mice elevated CT blood levels sixfold 30 min after glucose injection, which returned to baseline levels 90 min later. Wang *et al*. [43] demonstrated that a carbohydrate-rich diet boosted CT blood levels. In contrast, metyrapone (2-methyl-1,2-di-3-pyridyl-1-propanone), a glucocorticoid biosynthesis inhibitor, was shown to reduce ischemic brain injury, possibly by reducing blood CT levels [44–47].

Preischemic hyperglycemia: detriment or benefit

A recent study in rats is most revealing regarding the role that glucose plays in cerebral ischemia [48]. When rats were made hyperglycemic by glucose loading (2 g/kg, intraperitoneally) 15–60 min prior to a 7-min episode of cerebral ischemia, a significant increase in the degree of delayed neuronal damage postischemia was found in comparison with control, saline-injected rats (Fig. 1). In contrast, rats loaded with glucose 120–240 min preischemia, although also hyperglycemic at the onset of ischemia, showed a significantly lower degree of delayed neuronal damage postischemia in comparison with control rats. Hippocampal levels of lactate were measured at the end of the ischemic period in rats administered with either saline or glucose preischemia. The lactate levels measured were significantly and equally higher in rats administered glucose either 15 or 120 min preischemia when compared with control, saline-administered rats.

Figure 1



The effects of glucose administration (2 g/kg, intraperitoneally [i.p.]) on three different parameters. Blood glucose and corticosterone levels in samples taken from one group of rats at the time points indicated after glucose injection, and the degree of ischemic hippocampal damage (as measured 7 days postischemia) in another group of rats administered glucose at the same time points prior to induction of ischemia. Also shown are the effects of either metyrapone (100 μg/kg, i.p.) or mifepristone (RU486; 40 mg/kg, i.p.) on the degree of ischemic damage in rats that were administered glucose 15 min preischemia. *Significantly different from control, normoglycemic rats ($P < 0.05$); **significantly different from hyperglycemic rats injected with glucose 15 min preischemia ($P < 0.05$) using an unpaired *t* test.

These results contradict, and thus refute, the hypothesis that delayed ischemic neuronal damage is directly correlated with brain lactate levels. Our finding that inhibition of lactate utilization immediately postischemia is detrimental [49] further refutes the lactic acidosis hypothesis. Thus, in those cases where high brain levels of lactate were detected 30–90 min after the onset of reperfusion [1,50–58], lactate probably remained unused due to cell death.

Since neither glucose nor lactate appears to be the damaging factor during cerebral ischemia, we postulated that glucose loading evokes a short-lived (30–60 min) systemic response (hormonal or other) that, when occurring simultaneously with an ischemic episode, is capable of aggravating the degree of delayed neuronal damage postischemia. Allowing this short-lived systemic response to subside (120 min) prior

to the onset of the ischemic episode would make apparent the protective effect of glucose on the ischemic brain (Fig. 1). This glucose-induced protection stems from both hyperglycemic supplies of the sugar to sustain anaerobic glycolysis and from the ample supplies of lactate available for oxidation on reperfusion/reoxygenation.

Corticosterone: a systemic factor released in response to glucose administration

Preliminary experiments to test the effects of glucose loading on plasma CT levels revealed a sharp increase in the level of this stress hormone 15–30 min after glucose administration, followed by a return to baseline level 120 min after glucose administration [48]. These changes appear to correlate with the aggravation of neuronal damage by hyperglycemia when induced 15 min preischemia, and by the lack of such aggravation when glucose is administered 120 min preischemia.

These preliminary results support the postulate by which the glucose paradox is an outcome of glucose-induced increase in CT levels that lasts for approximately 60 min (see also [42]). While the observed changes in plasma CT levels in response to glucose loading do correlate with the postischemic outcome, such correlation by itself does not provide the proof that CT is the culprit of the glucose paradox phenomenon. A more direct approach must be taken to demonstrate the complicity of CT. Hence, either blockade of CT biosynthesis, on the one hand, or antagonism of its receptor, on the other, or both, would provide stronger supportive evidence if and when these approaches could abolish the aggravating effect of preischemic hyperglycemia.

Chemical adrenalectomy, using metyrapone, is one way to inhibit CT biosynthesis. Preliminary experiments with metyrapone [48] support the notion that glucose-induced CT release is the culprit behind the glucose paradox. As can be seen from Figure 1, rats pretreated with metyrapone suffered no aggravation of neuronal damage when administered glucose 15 min preischemia. These rats actually exhibited a degree of ischemic damage that was significantly lower than the damage measured in control, normoglycemic rats. This indicates that, once the aggravating factor (i.e. CT) is removed, glucose can be beneficial even when loaded shortly preischemia. The blood glucose levels of metyrapone-treated, glucose-loaded rats just prior to the ischemic episode were as high as those of untreated rats loaded with glucose.

The second approach, antagonizing CT action at its receptor, was also tested. For that purpose, the glucocorticoid receptor antagonist mifepristone (RU486) [59] was used. Glucose-loaded rats (15 min preischemia) treated with the antagonist (40 mg/kg, intraperitoneally) 45 min preischemia exhibited a significantly lower degree of postischemic damage than glucose-loaded rats untreated with RU486. The damage was indistinguishable from that measured in control, normoglycemic rats (unpublished data).

When the findings of the glucose-induced, short-lived increase in CT release and of the abilities of both metyrapone and RU486 to abolish the preischemic hyperglycemia-aggravated postischemic damage are taken together, they unequivocally point at CT as the culprit behind the glucose paradox of cerebral ischemia. The CT hypothesis is consequently being offered to explain this paradox instead of the lactic acidosis hypothesis.

Summary

The glucose paradox of cerebral ischemia, the phenomenon of preischemic hyperglycemia-aggravated postischemic outcome, has been blamed on the accumulation of lactate and the intensification of acidosis. This explanation has recently been questioned with several data.

Data have shown that lactate is an excellent aerobic energy substrate in the brain, and a crucial one during recovery from ischemia. It is therefore an unlikely detrimental factor in cerebral ischemia.

Glucose, the only readily available energy substrate in the brain under normoxic conditions, has been shown as the only substrate that could sustain ion homeostasis, at least for a while, during an ischemic episode. Yet, when administered shortly (15–60 min) preischemia, an aggravation of the ischemic outcome is observed. When administered 2–3 hours preischemia, however, despite the presence of hyperglycemic conditions, no aggravation of the outcome was observed. Hence, glucose *per se* is an unlikely aggravator of ischemic damage.

It has been shown that glucose loading induces a short-lived (~60 min), several-fold increase in CT plasma levels, a stress hormone known to aggravate the outcome of metabolic insults. It has also been shown, however, that pretreatment of rats with metyrapone, an inhibitor of CT biosynthesis, abolished the postischemic aggravating effect of glucose when loaded shortly preischemia. Finally, RU486 (an antagonist of the CT receptor) was also shown to abolish the aggravating effect of glucose loading shortly preischemia.

It is hypothesized that glucose-induced CT release, when occurring shortly preischemia, is the event responsible for the phenomenon known as the glucose paradox of cerebral ischemia. Neither lactate nor glucose *per se* has anything to do with this phenomenon. Both investigators and clinicians are encouraged to re-examine their notions and clinical practices regarding the roles of glucose in cerebral ischemia (stroke).

Competing interests

None declared.

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