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Research Report

Levels of S100B in brain and blood of rats with diabetic ketoacidosis

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ABSTRACT

Diabetic ketoacidosis (DKA) frequently causes subtle brain injuries in children. Rarely, these injuries can be severe and life threatening. The physiological processes leading to brain injury during DKA are poorly understood. S100B is a calcium-binding protein secreted by astrocytes. Elevated serum S100B levels are documented in several types of brain injuries. S100B may have either neuroprotective or neurotoxic effects, depending upon the concentration. We undertook the current studies to measure alterations in S100B production and secretion during DKA. We measured serum S100B concentrations in juvenile rats during and after DKA, and used immunohistochemistry to measure S100B expression in the hippocampus, cortex and striatum. Compared to levels in both normal and hyperglycemic control rats, serum S100B levels during DKA were significantly reduced. Serum S100B gradually rose after DKA, returning to levels of hyperglycemic controls by 72 h. S100B expression in the hippocampus was also significantly reduced 24 h after DKA. There were no significant changes in S100B expression in other brain regions. Our findings contrast with those for other types of brain injuries in which both serum S100B levels and astrocyte S100B expression are typically elevated. These data suggest that serum S100B measurement cannot be used as an indicator of brain injury during DKA. Whether reduced S100B production or secretion is involved in the pathogenesis of DKA-related brain injury should be investigated.

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1. Introduction

S100B is a calcium binding protein that is produced and secreted predominantly by astrocytes in the brain. S100B is thought to interact with a large number of target proteins thereby participating in numerous astrocytic functions including regulation of cell proliferation and differentiation, calcium homeostatsis, enzyme activity and other functions (Donato et al., 2009; Goncalves et al., 2008). S100B is also actively secreted by astrocytes in response to multiple stimuli. At low concentrations, S100B has neuroprotective effects, but at high concentrations S100B is neurotoxic (Donato et al., 2009; Goncalves et al., 2008). Regulation of S100B expression and secretion is complex and the details of this regulation are not fully understood (Donato et al., 2009; Goncalves et al., 2008; Filippidis et al., 2010).

Many types of brain injury are associated with increased serum levels of S100B, but it is unclear whether this rise in S100B is due to release from damaged cells or from increased S100B production under pathological conditions (Filippidis et al., 2010). Furthermore, it is unclear whether S100B enters the serum as a result of blood–brain barrier disruption or via secretion into the CSF. It has been proposed that measurement of serum levels of S100B could be used as a clinical biomarker of brain injury. Serum S100B measurement has been shown to be a sensitive indicator of traumatic brain injury (Goncalves et al., 2008; Filippidis et al., 2010; Marchi et al., 2013) but the sensitivity of S100B measurement for detecting other types of brain injury is less well described.

Children with diabetic ketoacidosis (DKA) frequently have radiographic evidence of subtle brain edema, and studies involving neurocognitive testing suggest that DKA also causes neurocognitive deficits, particularly memory dysfunction (Ghetti et al., 2010; Glaser et al., 2012, 2013, 2006). In rare cases, DKA-related brain edema and brain injury can be severe or even life threatening. Whether circulating biomarkers, such as S100B, could be used to detect brain injury in children with DKA is unknown. We undertook the current study to evaluate serum S100B levels as well as brain expression of S100B during diabetes as well as during DKA in a rat model.

2. Results

We evaluated juvenile rats with DKA (1) before treatment with insulin and saline, (2) after 4 h of insulin and saline treatment, (3) 24 h after recovery from DKA, and (4) 72 h after recovery from DKA. We measured serum S100B concentrations in these groups as well as brain S100B expression. These results were compared to those of healthy control rats and rats with diabetes without DKA exposure (hyperglycemic control rats).

2.1. Biochemical values in DKA groups and control groups

Biochemical values for rats in each of the experimental groups used for measurement of brain S100B expression are shown in Tables 1 and 2. Biochemical data for rats used for serum S100B measurements were similar (see Appendix Tables A1 and A2).

2.2. Serum S100B concentrations (Fig. 1)

During DKA (untreated DKA, UD), S100B values were significantly lower than those for both healthy control rats and hyperglycemic rats. Significantly decreased S100B values persisted during DKA treatment and 24 h after treatment of DKA (D4 and D24 respectively). By 72 h after DKA treatment, S100B values had returned to levels similar to those of hyperglycemic rats, but remained significantly lower than those of healthy control rats.

2.3. Brain S100B expresssion

When we evaluated S100B expression in rat brain specimens using immunohistochemical staining, we found that hyperglycemia alone did not significantly alter S100B expression compared to measurements in healthy control rats (Fig. 2). Brain S100B expression also was not significantly changed during untreated DKA, however, significant declines in brain S100B expression were observed in the hippocampus 24 h after DKA treatment in comparison with hyperglycemic controls. Similar but slightly smaller sample mean reductions of brain S100B expression during and 72 hours after DKA treatment in both the hippocampus and the cortex were not statistically significantly different from 0 in this small sample. Decreased astrocyte expression of S100B was in contrast to the significantly increased expression of glial fibrillary acidic protein (GFAP) during DKA documented in previous studies by our group (Fig. 3) (Lo et al., 2015).

3. Discussion

S100B is abundant in the brain and is constitutively produced by astrocytes (Donato et al., 2013; Sorci et al., 2011; Zhang et al., 2011) which are also the main source of circulating S100B (Goncalves et al., 2008). S100B exerts regulatory effects in the brain via both intracellular and extracellular actions (Donato et al., 2009). The Receptor for Advanced Glycation End Products (RAGE) is the main ligand for S100B (Bianchi et al., 2010, 2011; Steiner et al., 2009). Whether S100B binding to RAGE promotes beneficial or detrimental effects varies based on its concentration, with low concentrations promoting neuroprotection and high concentrations promoting inflammation and detrimental effects (Donato et al., 2009).

In the current study, we found that serum S100B concentrations in juvenile rats were significantly decreased during and 24 h after DKA, and that S100B expression in the hippocampus was significantly decreased 24 h after DKA. These declines were not related to astrocyte loss because expression of GFAP is significantly increased during the same period, as shown in our previous work (Lo et al., 2015). These data are important for several reasons. Because S100B is produced mainly by astrocytes, measurement of circulating S100B has been proposed as an indicator of brain injury (Goncalves et al., 2008; Filippidis et al., 2010; Marchi et al., 2013). Our data suggest, however, that elevation in the serum