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Hypothesis

Calpain in Acute Hepatic Encephalopathy: A Player in Pathophysiology and a Possible Target for Pharmacological Intervention

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Abstract

Acute hepatic encephalopathy (AHE) is a rapidly worsening neuropsychiatric syndrome, secondary to acute liver failure (ALF). In most cases, AHE is fatal without liver transplantation. Extending the survival of AHE patients is clinically important, hoping to find appropriate livers for transplantation. Neuroprotection and hepatoprotection can offer future prospects to achieve this goal. Ammonia which is increased in the brain of AHE patients stimulates the activity of N-methyl-D-aspartatre (NMDA) receptors. Based on animal studies reporting beneficial effects of inhibition of these receptors, we hereby suggest that calpain, a Ca^{2+} -dependent proteolytic enzyme and a downstream mediator of cell injury conferred by over-stimulation of NMDA receptors, can play role in the pathogenesis of brain injury in AHE. Moreover, in this hypothesis, calpain has been proposed as a potential target to save neurons from injury in AHE. Inhibition of calpain might have a concomitant hepatoprotective effect too, and so, inhibition of calpain might offer a good pharmacological strategy for protecting both liver and brain and increasing the survival time in AHE patients. We have suggested several methods to prove our hypothesis experimentally.

Keywords: Acute hepatic encephalopathy; Neuroprotection; Hepatoprotection; Calpain; Calpain inhibition

Introduction

Acute liver failure (ALF) can precipitate a rapidly worsening neurological syndrome which is clinically called acute hepatic encephalopathy (AHE)[1]. Patients suffering from this critical condition are highly susceptible to death. Liver transplantation is the only effective therapeutic intervention to save the lives of the AHE patients [2]. Unfortunately, for many patients, appropriate livers are not available before the disease being irreversibly fatal. So finding novel therapeutic targets for extending the survival time of AHE patients is attractive [3].

In experimental studies, N-methyl-D-aspartatre (NMDA) receptors have been reported to play role in the pathogenesis of AHE [4,5]. Inhibition of these receptors has been effective in decreasing the disease severity and increasing the survival time of AHE animals [6,7]. NMDA receptors are ionotropic glutamate receptors which upon over-activation, cause death of neurons in several acute brain insults and chronic neurodegenerative diseases [8]. Glutamate is increased in the CNS in AHE and stimulates NMDA receptors [9]. Moreover, increased levels of ammonia due to lack of hepatic detoxification in AHE is suspected to contribute to the pathophysiology [10] leading to brain dysfunction [11,12]. It has been suggested that ammonia stimulates the activity of NMDA receptors [11] and by this mechanism, can cause neural cell toxicity. To elucidate the exact mechanism for NMDA receptor-mediated cell injury in AHE, the post-receptor signaling machinery of NMDA receptor should be considered. The current hypothesis has been proposed to offer a new pathophysiological aspect of cellular toxicity and to suggest a novel pharmacological target for treatment of AHE (Figure 1).

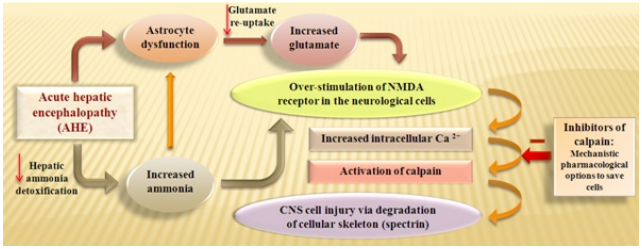

Figure 1: During the pathophysiology of encephalopathy in AHE, increased activity of calpain is a consequence of NMDA-mediated Ca 2+ overload. Elevated glutamate over-stimulates NMDA receptors. Ammonia which is elevated in AHE stimulates the NMDA receptor also. Calpain degrades structural proteins and plays a pivotal role in neural cell death. Inhibition of calpain can provide a pharmacological target to save cells in the CNS.

Hypothesis

There are several lines of evidence that over-stimulation of NMDA receptors results in massive and durable influx of Ca^{2+} into the cells [13,14]. In many diseases, high levels of intracellular Ca^{2+} can activate the Ca^{2+}-dependent proteolytic enzyme, calpains [15]. Calpain degrades many cellular proteins including structural proteins of the cytoskeleton [16,17]. We suggest that calpain activity is increased in neurons and other CNS cells during AHE. Importantly, inhibition of calpain is proposed as a therapeutic approach in this disease.

Evaluation of the hypothesis

Calpain contributes to neuronal cell death in acute neurological insults such as cerebro-vascular attack [18], traumatic brain injury [19] and spinal cord injury [20]. In all these cases, glutamate-induced NMDA receptor over-stimulation can be a major cause for calpain activation [21,22]. In AHE, we propose that calpain is activated as a consequence of NMDA receptor stimulation. NMDA receptor

stimulation is the result of elevated level of glutamate and ammonia in AHE.

To evaluate our hypothesis AHE patient's cerebrospinal fluid (CSF) and brains autopsies of patients died due to AHE might be studied to see if calpain is over-activated in AHE compared to controls. In vivo AHE animal models are also very invaluable for investigation of the pathophysiology and pharmacology of AHE [3,23]. Cerebral calpain activity can be studied by means of biological and histopathological methods such as western blot and immunohistochemistry [24,25]. In AHE animals, the effect of several calpain inhibitors can be studied [26].

Consequences of the Hypothesis and Discussion

There are few valid pharmacological targets to protect the CNS in AHE. In this hypothesis, calpain is suggested as an executor of cell injury in AHE. Over-activation of NMDA receptors by ammonium and glutamatecauses Ca^{2+} influx into the cells. Subsequently, calpain would be activated. In many disease states, calpain has been targeted as a potential pharmacological target. Traumatic brain injury, spinal cord injury, cerebrovascular attack, multiple sclerosis and other diseases could be mentioned as states in which calpain have been experimentally inhibitedand the strategy has been successful as neuroprotective intervention [26]. Consequently, inhibition of calpain in AHE must be an effective neuroprotective strategy. Furthermore, the pathological activation of calpain has been reported to play role in progression of liver injury in toxin-mediated hepatotoxicity models [27,30]. Socalpain inhibition in AHE, might provide concomitant hepatoprotective benefits too. So our hypothesis can offer a concurrent neuro- and hepatoprotective strategy to extend the survival period of AHE patients. As a consequence the patients can have either more opportunity of liver function recovery or more time to find appropriate livers for transplantation.

Conflict of Interest Statement

None declared.

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