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Cerebrospinal fluid hypoxanthine, xanthine and uric acid levels may reflect glutamate-mediated excitotoxicity in different neurological diseases

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Abstract

Glutamate-mediated excitotoxicity is associated with adenosine triphosphate (ATP) degradation and generation of oxygen radicals. Hypoxanthine and lactate depict energetic impairment, while xanthine and uric acid reflect activity of radical producing xanthine oxidase. Cerebrospinal fluid (CSF) glutamate, hypoxanthine, lactate, xanthine, and uric acid were investigated in neurological patients. In multiple sclerosis, myelopathy, stroke, epilepsy and viral meningitis glutamate, hypoxanthine, xanthine, and uric acid are increased 2–3-fold compared to controls. Lactate is only elevated in meningitis. Normal lactate dehydrogenase (LDH) levels and absent correlation between the albumin ratio and neurochemical parameters exclude an artificial increase due to cell lysis and barrier damage. Absent correlation between neurochemical parameters within each patient group is most likely related to preserved glial and neuronal uptake mechanisms. CSF hypoxanthine, xanthine, and uric acid levels appear superior to lactate in reflecting glutamate-mediated excitotoxicity in neurological patients. © 1997 Elsevier Science Ireland Ltd.

Keywords: Glutamate; Hypoxanthine; Xanthine; Uric acid; Oxygen free radicals; Lactate; Cerebrospinal fluid; Adenosine triphosphate

Glutamate is crucial in the pathophysiology of neurological diseases associated with functional and metabolic impairment of glial and neuronal cells [22]. Increased extracellular glutamate due to excessive release, abnormal leakage, or disturbed uptake becomes toxic by activating ionotropic and metabotropic glutamate receptors. Resulting derangement of ionic homeostasis, activation of second messenger systems, development of acidosis, production of oxygen free radicals and perturbation of energetic stability are signs of glutamate-mediated excitotoxicity [21,22]. Glutamate-mediated energy deprivation is associated with increased glucose consumption, production of lactate, and sustained adenosine triphosphate (ATP) degradation [6] leading to reversal of neuronal glutamate transport [13], synaptosomal leakage of glutamate [5] and increased neuronal vulnerability due to failure of ATP-dependent pump processes [14]. Degradation of intracellular high-energy phosphates is reflected by increased extracellular hypoxanthine and xanthine levels [9]. Direct coupling of excitotoxicity and ATP degradation is shown by successfully inhibiting elevation of ATP catabolites upon blocking *N*-methyl-D-aspartate receptors [7].

Glutamate-induced activation of various free radical generating systems (e.g. phospholipase A_2 and xanthine oxidase) results in marked production of oxygen free radicals [4], which among others have been shown to enhance glutamate-mediated excitotoxicity by reducing glial [19] and neuronal uptake of glutamate [1].

Detection of free radical production in brain is limited by the instability and short half-life of free radicals. Therefore, analysis of stable parameters is required as an indirect estimate of oxidative stress. For this, measurement of uric acid is used to reflect activity of xanthine oxidase with its sub-

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