Giselli Scaini[1], Gabriela Kozuchovski Ferreira[2], Emilio Luiz Streck[3,4]

Mechanisms underlying uremic encephalopathy

Mecanismos básicos da encefalopatia urêmica

1. PharmD, MSc student, Laboratório de Fisiopatologia Experimental, Programa de Pós-graduação em Ciências da Saúde, Universidade do Extremo Sul Catarinense. Criciúma (SC), Brazil.
2. PharmD, PhD student, Laboratório de Fisiopatologia Experimental, Programa de Pós-graduação em Ciências da Saúde, Universidade do Extremo Sul Catarinense. Criciúma (SC), Brazil.
3. PharmD, PhD, Laboratório de Fisiopatologia Experimental, Programa de Pós-graduação em Ciências da Saúde, Universidade do Extremo Sul Catarinense. Criciúma (SC), Brazil.
4. PharmD, PhD, Instituto Nacional de Ciência e Tecnologia Translacional em Medicina – INCT-TM - Universidade do Extremo Sul Catarinense - Criciúma (SC), Brazil.

Received from Laboratório de Fisiopatologia Experimental, Programa de Pós-graduação em Ciências da Saúde, Universidade do Extremo Sul Catarinense. Criciúma (SC), Brazil.

Submitted on May 9, 2010
Accepted on June 15, 2010

Author for correspondence:
Emilio Luiz Streck
Av. Universitária, 1105
Zip Code: 88806 - 000 - Criciúma (SC), Brazil
Phone: +55 (48) 3431-2539
E-mail: emiliostreck@gmail.com

ABSTRACT

In patients with renal failure, encephalopathy is a common problem that may be caused by uremia, thiamine deficiency, dialysis, transplant rejection, hypertension, fluid and electrolyte disturbances or drug toxicity. In general, encephalopathy presents with a symptom complex progressing from mild sensorial clouding to delirium and coma. This review discusses important issues regarding the mechanisms underlying the pathophysiology of uremic encephalopathy. The pathophysiology of uremic encephalopathy up to now is uncertain, but several factors have been postulated to be involved; it is a complex and probably multifactorial process. Hormonal disturbances, oxidative stress, accumulation of metabolites, imbalance in excitatory and inhibitory neurotransmitters, and disturbance of the intermediary metabolism have been identified as contributing factors. Despite continuous therapeutic progress, most neurological complications of uremia, like uremic encephalopathy, fail to fully respond to dialysis and many are elicited or aggravated by dialysis or renal transplantation. On the other hand, previous studies showed that antioxidant therapy could be used as an adjuvant therapy for the treatment of these neurological complications.

Keywords: Renal failure/complications; Uremia/complications; Brain diseases/etiology; Brain diseases/physiopathology; Uremia/complications

INTRODUCTION

As a consequence of the numerous advances in early diagnosis and treatment of several diseases, critical care has developed as a subspecialty in all clinical disciplines engaged in life-threatening diseases. In neurology, this leads to an increase of neurological critical care units dealing with a broad spectrum of vascular – infectious – immunological and metabolic diseases and malignancies not only as primary diseases of the central and peripheral nervous systems and muscle but also as secondary affections caused by other organ or systemic diseases.[1]

Acute renal failure (ARF) is a common and critical clinical entity, which affects around 5% to 7% of all hospitalized patients.[2,3] It is associated with various medical problems, treatments, and procedures. Despite advances in medical care, ARF still carries a significant morbidity and a 20% to 70% mortality rate. Unfortunately, this has not improved during the past years because of sicker and older population.[4]

In patients with renal failure, encephalopathy is a common problem that may be caused by uremia, thiamine deficiency, dialysis, transplant rejection, hy-

pertension, fluid and electrolyte disturbances or drug toxicity.[5] In general, encephalopathy presents with a symptom complex progressing from mild sensorial clouding to delirium and coma. It is often associated with headache, visual abnormalities, tremor, asterixis, multifocal myoclonus, chorea and seizures. These signs fluctuate from day to day or sometimes from hour to hour.[6]

Uremic encephalopathy may accompany acute or chronic renal failure, but in patients with acute renal failure the symptoms are generally more pronounced and progress more rapidly.[6,7] Besides the general symptom complex of encephalopathy, focal motor signs and the "uremic twitch convulsive" syndrome can be seen.[6,8] Even in patients with neurologically asymptomatic chronic renal disease, impaired cognitive processing can be disclosed by event-related potentials. This review discusses important issues regarding the mechanisms underlying the pathophysiology of uremic encephalopathy.

PATHOPHYSIOLOGY OF UREMIC ENCEPHALOPATHY

The pathophysiology of uremic encephalopathy up to now is uncertain, but several factors have been postulated to be involved;[9] it is a complex and probably multifactorial process. Hormonal disturbances, oxidative stress, accumulation of metabolites, imbalance in excitatory and inhibitory neurotransmitters, and disturbance of the intermediary metabolism have been identified as contributing factors.[10]

Hormonal disturbances

Toxic effects of the parathyroid hormone (PTH) on the central nervous system (CNS) have been recently suggested.[9] Experiments with animals reported biochemical changes in the brain, especially in ARF models. In acute and in chronic renal failure, PTH level is elevated with concomitant elevated calcium content in the cerebral cortex. This hypothesis is supported by one study which demonstrated that brain calcium content abnormalities in dogs with renal failure can be prevented by parathyroidectomy, so these changes appear to be PTH-dependent.[11]

Oxidative stress

Reactive oxygen species (ROS) are considered to be one of the important mediators for the pathophysiology of uremic encephalopathy. Evidence for oxidative stress in chronic renal failure (CRF) was based on the elevation of lipid peroxidation products, as a result of damage to cell and organelles membranes.[12-15] Several studies demonstrated that these toxic products cause an inflammatory burden in CRF through the generation of an imbalance between increased production of ROS and limited or decreased antioxidant capacity.[16]

Nitric oxide (NO), originally identified as the endothelium derived relaxing factor, now is known to be a critical intra- and intercellular signal molecule which plays a fundamental role in regulation of a wide variety of biologic functions.[17] In addition to its important physiologic functions, NO is involved in various pathologic processes that lead to cytotoxicity.[18,19] In this regard, interaction of NO with ROS, especially superoxide anion, leads to the generation of highly reactive and cytotoxic byproducts, such as peroxynitrite, which can react with DNA, lipids, and proteins.[20,21] For instance, peroxynitrite reacts with free tyrosine and tyrosine residues in protein molecules to produce nitrotyrosine. Alternatively, ROS can activate tyrosine to form tyrosyl, a radical that, in turn, oxidizes NO to produce nitrotyrosine.[21,22] Furthermore, neuronal NO synthase (nNOS) expression is elevated in the brain of uremic rats.[23] It has benn hypothesized that the concomitant increase in ROS with elevated brain tissue nNOS expression in uremia may favor generation and accumulation of nitrotyrosine in the uremic brain. Western blot analysis revealed a marked increase in nitrotyrosine content in the cerebral cortex of the rats with CRF. It is also important to note that the immunohistological examination of the brain in the CRF group indicated an association of nitrotyrosine with neuronal processes and plasma membrane of cortical cells.[24]

Sener et al.[25] also reported increased lipid peroxidation, collagen content and myeloperoxidase activity and decreased reduced glutathione (GSH) levels. In this study, the results demonstrated that CRF in rats yields to oxidative injury in the renal tissue, as well as in the lung, heart and brain tissues. The observed tissue damages were accompanied by elevated serum levels of pro-inflammatory mediators (LTB_4, TNF-α, IL-1β and IL-6), while histological analyses verified the severity of CRF-induced systemic inflammatory response in all the studied tissues.

Several studies have revealed that oxidative stress and the formation of aminoglycoside–iron complexes through iron-dependent Fenton reaction have been proposed to be the major mechanisms in the development of gentamicin (GM)-induced ARF.[26,27] In a recent report, Petronilho et al. [28] demonstrated that GM-induced oxidative damage is an early event and occurs before any observed increase in urea and creatinine levels, suggesting that oxidative dam-

age is related to GM-induced kidney injury and that the association of *N*-acetylcysteine (NAC) with deferoxamine (DFX) is effective in preventing GM-induced kidney damage, and this effect is not solely related to its antioxidant potential.

Accumulation of metabolites

Renal failure leads to the accumulation of various uremic toxins. Among the candidate uremic toxins are several guanidine compounds (GCs), previously reported to be increased in uremic biological fluids and tissues.[10,29-32] Several GCs may play an important role in the etiology of uremic encephalopathy. Four GCs appeared to be substantially increased in serum, cerebrospinal fluid, and brain of uremic patients. These compounds are creatinine, guanidine, guanidinosuccinic acid (GSA), and methylguanidine (MG); they were shown to be experimental convulsants in brain concentrations similar to those found in the uremic brain.[33,34] These compounds also induced tonic-clonic convulsions in adult mice. GSA and MG were markedly more potent convulsants than guanidine and creatinine.[35]

The kynurenine (KYN) pathway is the major route for tryptophan metabolism in mammals; this amino-acid is converted into KYN, which is transformed into 3-hydroxykynurenine (3-HK), a metabolite that generate ROS.[36,37] Several studies reported the accumulation of KYN metabolites in the blood of animal submitted to CRF,[38-40] and in uremic patients.[41,42] Thus, it is conceivable that the KYN pathway may also be altered and plays an important role in uremic encephalophaty. Kynurenine (KYN) and 3-hydroxy-kynurenine (3-HK) may be important mediators of neurological dysfunctions observed both in uremic patients and animals. In previous studies, serious behavioral disturbances like decreased locomotor, exploratory and emotional activity of rats suffering from CRF were reported, which closely resemble those observed in uremic patients.[35]

Imbalance in excitatory and inhibitory neurotransmitters

Animal studies and isolated tissues have suggested the involvement of serotonine and catecholamine,[43-45] acetylcholine,[46] γ-amino-butyric acid (GABA) and glycine,[47] and excitatory amino acid[48,49] neurotransmitter systems in uremic encephalopathy. Renal failure also leads to a large number of biochemical alterations and metabolic derangements which may potentially underlie the behavioral deficits[50-52]. Activation of the excitatory *N*-methyl-d-aspartate (NMDA) receptors and concomitant inhibition of inhibitory GABA(A)-ergic neurotransmission have been proposed as underlying mechanisms. Moreover, guanidinosuccinic acid possibly inhibits transketolase, a thiamine-dependent enzyme of the pentose phosphate pathway that is important for the maintenance of myelin. Inhibition of transketolase is related to demyelinative changes which contribute to both central and peripheral nervous system changes in chronic uremia.[53]

Several studies also described a possible mechanism for the contribution of GCs to uremic hyperexcitability, referring to the *in vitro* effects of uremic GCs on inhibitory and excitatory amino acid receptors.[47,49,54-56] Some studies have been demonstrated GCs blocked GABA and glycine-evoked depolarization. GSA was shown to be the most potent compound, whereas MG, guanidine and creatinine blocked GABA and glycine responses less potently. These findings suggest that the uremic GCs might block the $GABA_A$ and glycine receptor-associated chloride channel.[47] Recent studies suggested that GSA, MG and creatinine may act as competitive antagonists at the transmitter recognition site of the $GABA_A$ receptor,[56] which was also shown in some other endogenous GCs with convulsive action.[53,57,58]

Disturbance of the intermediary metabolism

Animal studies and *in vitro* testing demonstrated disturbances of the intermediary metabolism with decreased levels of creatine phosphate, adenosine triphosphate (ATP) and glucose, and increased levels of adenosine monophosphate (AMP), adenosine diphosphate (ADP) and lactate. These changes are associated with a decrease in both brain metabolic rate and cerebral oxygen consumption and are consistent with a generalized decrease in brain energy use. Moreover, inhibition of cerebral Na^+,K^+-ATPase has been reported in experimental uremic animals.[7] Moreover, creatine kinase activity was inhibited in prefrontal cortex, cerebral cortex and hippocampus, brain areas that are crucial for cognitive processes in a model of uremic encephalopathy.[59] On the other hand, previous studies showed inhibition of respiratory chain complexes I and IV activities in experimental uremic animals.[60]

In this context, ROS may be related to an increase in mitochondrial membrane permeabilization. The rupture of mitochondrial membranes that leads to functional impairment of mitochondria and to the release of toxic mitochondrial intermembrane space proteins intro the cytosol, causing a profound bioenergetic and redox crisis and activates an ensemble of catabolic processes, ultimately leading to cell death.[61]

FINAL COMMENTS

Neurological complications whether due to the uremic state or its treatment, contribute largely to the morbidity and mortality in patients with renal failure. In patients with renal failure, encephalopathy is a common problem that probably involves several factors caused by uremia. Factors as hormonal disturbances, accumulation of metabolites, imbalance in excitatory and inhibitory neurotransmitters, and disturbance of the intermediary metabolism have been postulated to be involved in the pathophysiology of uremic encephalopathy. Moreover, induction of ROS generation seems to play a notable role in the pathophysiology of uremic encephalopathy.

Despite continuous therapeutic progress, most neurological complications of uremia, like uremic encephalopathy, fail to fully respond to dialysis and many are elicited or aggravated by dialysis or renal transplantation. On the other hand, previous studies showed that antioxidant therapy and cysteinyl leukotrienes (CysLTs) receptor antagonist could be used as an adjuvant therapy for the treatment of these neurological complications. More studies must be performed in order to elucidate the complex mechanisms involved in the pathophysiology of uremic encephalopathy. With this information, researchers will be able to create and suggest new treatments.

RESUMO

Em pacientes com insuficiência renal, a encefalopatia é um problema comum que pode ser provocado pela uremia, deficiência de tiamina, diálise, rejeição de transplante, hipertensão, desequilíbrios hidroeletrolíticos e toxicidades medicamentosas. Em geral a encefalopatia se apresenta como um complexo de sintomas que progride de uma leve obnubilação sensitiva até delírio e coma. Esta revisão discute questões importantes com relação aos mecanismos de base da fisiopatologia da encefalopatia urêmica. A fisiopatologia da encefalopatia urêmica é até hoje incerta, mas postula-se o envolvimento de diversos fatores; trata-se de um processo complexo e provavelmente multifatorial. Distúrbios hormonais, estresse oxidativo, acúmulo de metabólitos, desequilíbrio entre os neurotransmissores excitatórios e inibitórios, e distúrbio do metabolismo intermediário foram identificados como fatores contribuintes. A despeito do progresso continuado na terapêutica, a maior parte das complicações neurológicas da uremia, como a encefalopatia urêmica, não respondem plenamente à diálise e muitas delas são desencadeadas ou agravadas pela diálise ou transplante renal. Por outro lado, estudos prévios demonstraram que a terapia antioxidante pode ser utilizada como terapia coadjuvante para o tratamento destas complicações neurológicas.

Descritores: Insuficiência renal/complicações; Encefalopatias/etiologia; Encefalopatias/fisiopatologia; Uremia/complicações

REFERENCES

1. Kunze K. Metabolic encephalopathies. J Neurol. 2002;249(9):1150-9. Review.
2. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med. 1983;74(2):243-8.
3. Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis. 2002;39(5):930-6.
4. Singri N, Ahya SN, Levin ML. Acute renal failure. JAMA. 2003;289(6):747-51.
5. Mahoney CA, Arieff AI. Uremic encephalopathies: clinical, biochemical, and experimental features. Am J Kidney Dis. 1982;2(3):324-36.
6. Raskin NH. Neurological complications of renal failure. In: Aminoff MJ, editor. Neurology and general medicine. 2nd ed. New York: Churchill Livingstone; 1995. p. 303-19.
7. Burn DJ, Bates D. Neurology and the kidney. J Neurol Neurosurg Psychiatry. 1998;65(6):810-21.
8. De Deyn PP, Saxena VK, Abts H, Borggreve F, D'Hooge R, Marescau B, Crols R. Clinical and pathophysiological aspects of neurological complications in renal failure. Acta Neurol Belg. 1992;92(4):191-206. Review.
9. Fraser CL, Arieff AI. Metabolic encephalopathy as a complication of renal failure: mechanisms and mediators. New Horiz. 1994;2(4):518-26.
10. Vanholder R, De Smet R, Glorieux G, Argilés A, Baurmeister U, Brunet P, Clark W, Cohen G, De Deyn PP, Deppisch R, Descamps-Latscha B, Henle T, Jörres A, Lemke HD, Massy ZA, Passlick-Deetjen J, Rodriguez M, Stegmayr B, Stenvinkel P, Tetta C, Wanner C, Zidek W; European Uremic Toxin Work Group (EUTox). Review on uremic toxins: classification, concentration, and interindividual variability. Kidney Int. 2003;63(5):1934-43.
11. Guisado R, Arieff AI, Massry SG, Lazarowitz V, Kerian A. Changes in the electroencephalogram in acute uremia. Effects of parathyroid hormone and brain electrolytes. J Clin Invest. 1975;55(4):738-45.
12. Kishore BK, Gejyo F, Arakawa M. Lipid peroxidation uraemia: malondialdehyde: a putative uraemic toxin. IRCS Med Sci. 1983;11:750-1.
13. Trznadel K, Pawlicki L, Kedziora J, Luciak M, Blaszczyk J, Buczynski A. Superoxide anion generation, erythrocytes superoxide dismutase activity, and lipid peroxidation during hemoperfusion and hemodialysis in chronic uremic patients. Free Radic Biol Med. 1989;6(4):393-7.
14. Paul JL, Man NK, Moatti N, Raichvarg D. [Membrane phospholipid peroxidation in renal insufficiency and chronic hemodialysis]. Nephrologie. 1991;12(1):4-7. Review. French.

15. Vaziri ND, Oveisi F, Ding Y. Role of increased oxygen free radical activity in the pathogenesis of uremic hypertension. Kidney Int. 1998;53(6):1748-54.
16. Maruyama Y, Lindholm B, Stenvinkel P. Inflammation and oxidative stress in ESRD--the role of myeloperoxidase. J Nephrol. 2004;17 Suppl 8:S72-6. Review.
17. Turpaev KT. Nitric oxide in intercellular communication. Mol Biol (Mosk). 1998;32:475-84.
18. Hogg N, Kalyanaraman B. Nitric oxide and lipid peroxidation. Biochim Biophys Acta. 1999;1411(2-3):378-84. Review.
19. Murphy MP. Nitric oxide and cell death. Biochim Biophys Acta. 1999;1411(2-3):401-4-14. Review.
20. Beckman JS, Koppenol WH. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. Am J Physiol. 1996;271(5 Pt 1):C1424-37.
21. Halliwell B. What nitrates tyrosine? Is nitrotyrosine specific as a biomarker of peroxynitrite formation in vivo? FEBS Lett. 1997;411(2-3):157-60.
22. Eiserich JP, Butler J, van der Vliet A, Cross CE, Halliwell B. Nitric oxide rapidly scavenges tyrosine and tryptophan radicals. Biochem J. 1995;310(Pt 3):745-9.
23. Ye S, Nosrati S, Campese VM. Nitric oxide (NO) modulates the neurogenic control of blood pressure in rats with chronic renal failure (CRF). J Clin Invest. 1997;99(3):540-8.
24. Deng G, Vaziri ND, Jabbari B, Ni Z, Yan XX. Increased tyrosine nitration of the brain in chronic renal insufficiency: reversal by antioxidant therapy and angiotensin-converting enzyme inhibition. J Am Soc Nephrol. 2001;12(9):1892-9.
25. Sener G, Sakarcan A, Sehirli O, Ekşioğlu-Demiralp E, Sener E, Ercan F, et al. Chronic renal failure-induced multiple-organ injury in rats is alleviated by the selective CysLT1 receptor antagonist montelukast. Prostaglandins Other Lipid Mediat. 2007;83(4):257-67.
26. Maldonado PD, Barrera D, Rivero I, Mata R, Medina-Campos ON, Hernández-Pando R, Pedraza-Chaverrí J. Antioxidant S-allylcysteine prevents gentamicin-induced oxidative stress and renal damage. Free Radic Biol Med. 2003;35(3):317-24.
27. Karahan I, Atessahin A, Yilmaz S, Ceribaşi AO, Sakin F. Protective effect of lycopene on gentamicin-induced oxidative stress and nephrotoxicity in rats. Toxicology. 2005;215(3):198-204.
28. Petronilho F, Constantino L, de Souza B, Reinke A, Martins MR, Fraga CM, et al. Efficacy of the combination of N-acetylcysteine and desferrioxamine in the prevention and treatment of gentamicin-induced acute renal failure in male Wistar rats. Nephrol Dial Transplant. 2009;24(7):2077-82.
29. De Deyn PP, Marescau B, Cuykens JJ, Van Gorp L, Lowenthal A, De Potter WP. Guanidino compounds in serum and cerebrospinal fluid of non-dialyzed patients with renal insufficiency. Clin Chim Acta. 1987;167(1):81-8.
30. De Deyn PP, Marescau B, D'Hooge R, Possemiers I, Nagler J, Mahler C. Guanidino compound levels in brain regions of non-dialyzed uremic patients. Neurochem Int. 1995;27(3):227-37.
31. De Deyn P, Marescau B, Lornoy W, Becaus I, Lowenthal A. Guanidino compounds in uraemic dialyzed patients. Clin Chim Acta. 1986;157(2):143-50.
32. De Deyn P, Marescau B, Lornoy W, Becaus I, Van Leuven I, Van Gorp L, Lowenthal A. Serum guanidino compound levels and the influence of a single hemodialysis in uremic patients undergoing maintenance hemodialysis. Nephron. 1987;45(4):291-5.
33. De Deyn PP, Vanholder R, Eloot S, Glorieux G. Guanidino compounds as uremic (neuro)toxins. Semin Dial. 2009;22(4):340-5.
34. D'Hooge R, Pei YQ, Manil J, De Deyn PP. The uremic guanidine compound guanidinosuccinic acid induces behavioral convulsions and concomitant epileptiform electrocorticographic discharges in mice. Brain Res. 1992;598(1-2):316-20.
35. Topczewska-Bruns J, Tankiewicz A, Pawlak D, Buczko W. Behavioral changes in the course of chronic renal insufficiency in rats. Pol J Pharmacol. 2002;53(3):263-9.
36. Pawlak K, Domaniewski T, Mysliwiec M, Pawlak D. The kynurenines are associated with oxidative stress, inflammation and the prevalence of cardiovascular disease in patients with end-stage renal disease. Atherosclerosis. 2009;204(1):309-14.
37. Okuda S, Nishiyama N, Saito H, Katsuki H. 3-Hydroxykynurenine, an endogenous oxidative stress generator, causes neuronal cell death with apoptotic features and region selectivity. J Neurochem**.** 1998;70(1):299-307.
38. Pawlak D, Tankiewicz A, Mysliwiec P, Buczko W. Tryptophan metabolism via the kynurenine pathway in experimental chronic renal failure. Nephron. 2002;90(3):328-35.
39. Pawlak D, Tankiewicz A, Buczko W. Kynurenine and its metabolites in the rat with experimental renal insufficiency. J Physiol Pharmacol. 2001;52(4 Pt 2):755-66.
40. Pawlak D, Tankiewicz A, Matys T, Buczko W. Peripheral distribution of kynurenine metabolites and activity of kynurenine pathway enzymes in renal failure. J Physiol Pharmacol. 2003;54(2):175-89.
41. Pawlak D, Pawlak K, Malyszko J, Mysliwiec M, Buczko W. Accumulation of toxic products degradation of kynurenine in hemodialyzed patients. Int Urol Nephrol. 2001;33(2)**:**399-404.
42. Pawlak D, Koda M, Wolczynski S, Mysliwiec M , Buczko W. Mechanism of inhibitory effect of 3-hydroxykynurenine on erythropoiesis in patients with renal insufficiency. Adv Exp Med Biol. 2003;527:375-80.
43. Ksiazek A, Solski J. Noradrenaline turnover in the tissues of uraemic rats. Int Urol Nephrol. 1990;22(1):89-93.
44. Ali F, Tayeb O, Attallah A. Plasma and brain catecholamines in experimental uremia: acute and chronic studies. Life Sci. 1985;37(19):1757-64.

45. Schmid G, Bahner U, Peschkes J, Heidland A. Neurotransmitter and monoaminergic amino acid precursor levels in rat brain: effects of chronic renal failure and malnutrition. Miner Electrolyte Metab. 1996;22(1-3):115-8.
46. Ni Z, Smogorzewski M, Massry SG. Derangements in acetylcholine metabolism in brain synaptosomes in chronic renal failure. Kidney Int. 1993;44(3):630-7.
47. De Deyn PP, Macdonald RL. Guanidino compounds that are increased in cerebrospinal fluid and brain of uremic patients inhibit GABA and glycine responses on mouse neurons in cell culture. Ann Neurol. 1990;28(5):627-33.
48. D'Hooge R, Pei YQ, De Deyn PP. N-methyl-D-aspartate receptors contribute to guanidinosuccinate-induced convulsions in mice. Neurosci Lett. 1993;157(2):123-6.
49. D'Hooge R, Raes A, Lebrun P, Diltoer M, Van Bogaert PP, Manil J, et al. N-methyl-D-aspartate receptor activation by guanidinosuccinate but not by methylguanidine: behavioural and electrophysiological evidence. Neuropharmacology. 1996;35(4):433-40.
50. Ringoir S, Schoots A, Vanholder R. Uremic toxins. Kidney Int Suppl. 1998;24:S4-9.
51. Moe SM, Sprague SM. Uremic encephalopathy. Clin Nephrol. 1994;42(4):251-6.
52. Vanholder R. Uremic toxins. Adv Nephrol Necker Hosp. 1997;26:143-63. Review.
53. De Deyn PP, D'Hooge R, Van Bogaert PP, Marescau B. Endogenous guanidino compounds as uremic neurotoxins. Kidney Int Suppl. 2001;78:S77-83.
54. D'Hooge R, Manil J, Colin F, De Deyn PP. Guanidinosuccinic acid inhibits excitatory synaptic transmission in CA1 region of rat hippocampal slices. Ann Neurol. 1991;30(4):622-3.
55. Giovannetti S, Cioni L, Balestri PL, Biagini M. Evidence that guanidines and some related compounds cause haemolysis in chronic uraemia. Clin Sci. 1968;34(1):141-8.
56. D'Hooge R, De Deyn PP, Van de Vijver G, Antoons G, Raes A, Van Bogaert PP. Uraemic guanidino compounds inhibit gamma-aminobutyric acid-evoked whole cell currents in mouse spinal cord neurones. Neurosci Lett. 1999;265(2):83-6.
57. Mori A. Biochemistry and neurotoxicology of guanidino compounds. History and recent advances. Pavlov J Biol Sci. 1987;22(3):85-94. Review.
58. D'Hooge R, Pei YQ, Marescau B, De Deyn PP. Convulsive action and toxicity of uremic guanidine compounds: behavioral assessment and relation to brain concentration in adult mice. J Neurol Sci. 1992;112(1-2):96-105.
59. Di-Pietro PB, Dias ML, Scaini G, Burigo M, Constantino L, Machado RA, et al. Inhibition of brain creatine kinase activity after renal ischemia is attenuated by N-acetylcysteine and deferoxamine administration. Neurosci Lett. 2008;434(1):139-43.
60. Barbosa PR, Cardoso MR, Daufenbach JF, Goncalves CL, Machado RA, Roza CA, et al. Inhibition of mitochondrial respiratory chain in the brain of rats after renal ischemia is prevented by N-acetylcysteine and deferoxamine. Metab Brain Dis. 2010;25(2):219-25.
61. Galluzzi L, Blomgren K, Kroemer G. Mitochondrial membrane permeabilization in neuronal injury. Nat Rev Neurosci. 2009;10(7):481-94. Review.