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Uremic Encephalopathy

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1. Introduction

Patients with renal failure often have signs and symptoms related to fluid and electrolyte disturbances, anemia, malnutrition, bone disease and gastrointestinal problems. One of those complications is the uremic encephalopathy. With the introduction of dialysis and renal transplantation, the incidence and severity of uremic encephalopathy have declined, but many patients fail to fully respond to dialytic therapy. 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 (Mahoney & Arieff, 1982). In this chapter, the symptoms, pathophysiology and treatment of uremic encephalopathy will be discussed. Other neurological complications of renal failure are not discussed in this chapter, but were recently reviewed (Brouns & De Deyn, 2004).

2. Clinical presentation

Uremic encephalopathy may accompany any form of severe acute or chronic renal failure. The clinical features appear to be related to the rate of development of renal failure. In patients with acute renal failure the symptoms are generally more pronounced and progress more rapidly than in patients with chronic renal failure (Aminoff, 1995; Burn & Bates, 1998).

The symptoms begin insidiously and are often not noticed by the patients but by their family members or caregivers. Most encephalopathies are reversible, making prompt recognition and treatment important. After hemodialysis, significant improvement of uremic encephalopathy occurs, but the level of azotemia correlates poorly with the degree of neurological dysfunction (Burn & Bates, 1998).

2.1 Mental status

Encephalopathy is a global cerebral dysfunction, often in the absence of primary structural brain disease. Nevertheless, in some contexts it can also lead to permanent brain injury, while in other cases it is reversible. It can be due to direct injury to the brain, or illness remote from the brain. In medical terms it can refer to a wide variety of brain disorders with very different etiologies, prognoses and implications.

Uremic encephalopathy usually presents with alterations in mental status fluctuating from mild sensorial clouding to delirium and coma. Impaired attention can be tested by simple

bedside tasks such as serial subtraction or naming months of the year in reverse. Other common findings include a disturbed sleep-wake cycle, decreased alertness, hypervigilance, hallucinations, sensory misperceptions, impaired memory and disorientation. The thought process is often disorganized and conversation is confused. Apathy, fatigue, irritability and inattentiveness are usually the initial symptoms while confusion, disturbances of sensory perception, hallucinations and stupor appear later. The level of alertness reflects the severity of the encephalopathy, coma being the most serious stage (Chen, 1996; Earnest, 1993).

2.2 Associated symptoms

Besides the alterations in mental status, other associated symptoms are often present. Clouding of the sensorium is almost always associated with mild diffuse weakness and a variety of motor disturbances. Tremor is common, but other involuntary movements such as fasciculations, multifocal myoclonus, chorea, asterixis or seizures are seen in patients at various times. Tremor is usually coarse and irregular at a rate of 8-10 Hz. Asterixis or flapping tremor is a dramatic problem, with jerking movements arising from lapses of posture holding, as of the outstretched hands. It is almost always bilateral. Unilateral asterixis suggests an occult structural lesion. Multifocal myoclonus is characterized by sudden, non-rhythmic, gross muscle twitching, particularly involving the face and the proximal muscles (Chen, 1996).

Besides the general symptom complex of encephalopathy, headache, focal motor signs and the “Uremic twitch convulsive” syndrome can be observed (Aminoff, 1995; De Deyn et al., 1992b). Focal neurological signs such as hemiparesis, dysarthria, visual abnormalities or reflex asymmetry tend to be transient and alternate from side to side (Bolton, 1990). Other common associated symptoms include uremic polyneuropathy, pruritus -often leading to self induced skin lesions-, and restless-legs syndrome. All these signs fluctuate from day to day or sometimes from hour to hour (Aminoff, 1995).

3. Diagnostic investigations

A laboratory investigation for encephalopathy includes a complete blood count, electrolyte panel and examination of glucose, urea, creatinine, liver enzymes and ammonia. No laboratory value, including specific evaluations of the renal function, correlates well with clinical symptoms and signs of uremia. Lumbar puncture often reveals elevated protein and occasionally a mild pleocytosis. A lumbar puncture is primarily performed to exclude an infectious cause of encephalopathy. CT or MRI of the head are only indicated when focal signs are present on physical examination and to exclude the presence of a subdural hematoma, ischemic stroke or hydrocephalus. Electroencephalographic (EEG) findings in uremic encephalopathy are non-specific but correlate with clinical symptoms and, therefore, may be of diagnostic value. In addition, it can be useful to exclude other causes of confusion such as infection or structural abnormalities. The most common EEG finding is a generalized slowing of the normal background. Intermittent frontal rhythmic theta activity and paroxysmal, bilateral, high voltage delta waves are also frequent. Sometimes bilateral spike-waves complexes or triphasic waves in the frontal regions are found (Fig. 1). Convulsions are often a late stage manifestation of chronic renal failure. Seizures are usually generalized tonic-clonic convulsions. Nevertheless, focal motor seizures are not uncommon. Epilepsia partialis continua may occur without generalized seizures (Brenner, 1985).

In patients with neurologically asymptomatic chronic renal disease, impaired cognitive processing can be disclosed by event-related potentials. Increase in P3 latency and decrease in P3 amplitude is found (Aminoff, 1995; Burn & Bates, 1998).

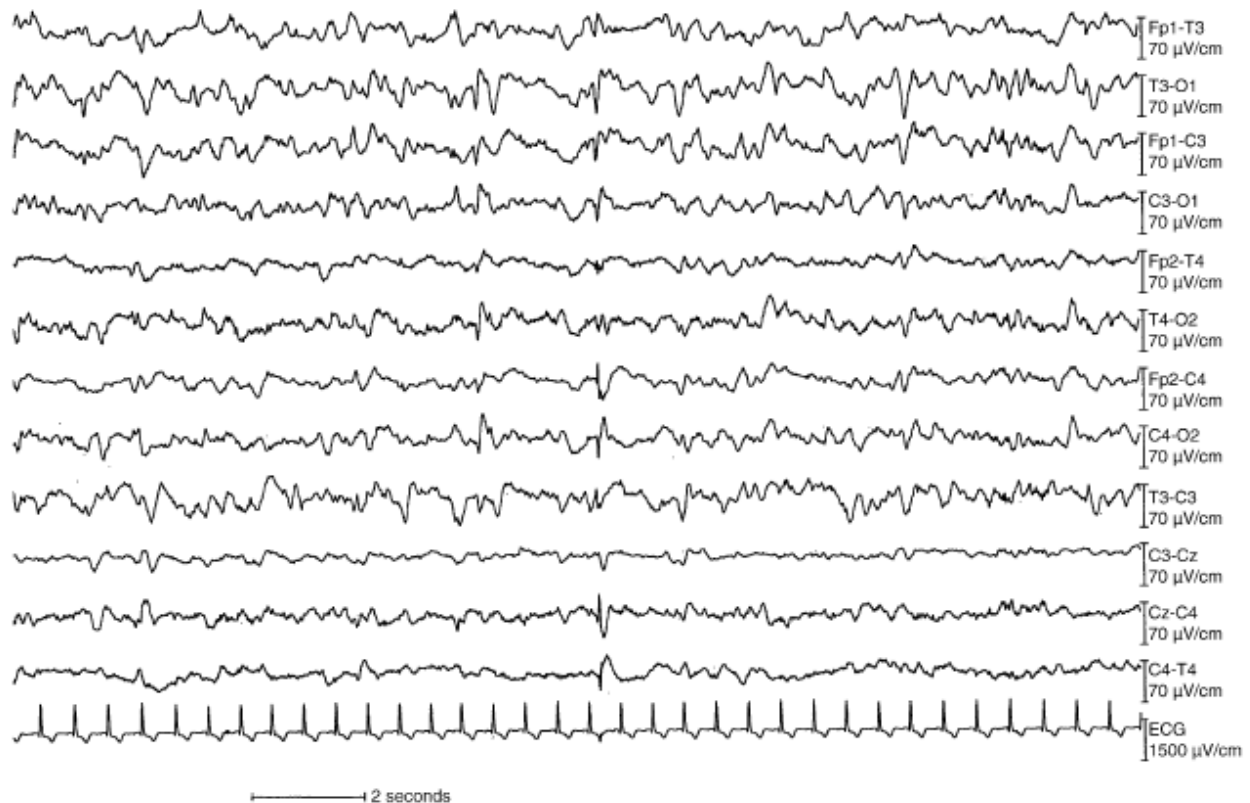


Fig. 1. Electroencephalographic findings in a patient with uremic encephalopathy, showing generalized slowing with an excess of delta and theta waves and bilateral spikes.

4. Pathophysiology

All forms of acute toxic-metabolic encephalopathy interfere with the function of the ascending reticular activating system and its projections to cerebral cortex, leading to impairment of arousal and awareness (Plum, 1982). The neurophysiologic mechanisms of encephalopathy include interruption of polysynaptic pathways and altered excitatory-inhibitory amino acid balance. Accumulation of metabolites, hormonal disturbance, disturbance of the intermediary metabolism and imbalance in excitatory and inhibitory neurotransmitters have been identified as contributing factors.

4.1 Uremic toxins

Renal failure results in accumulation of numerous organic substances that possibly act as uremic neurotoxins, but no single metabolite has been identified as the sole cause of uremia (Vanholder et al., 2003b). Symptoms are usually alleviated by dialysis or successful renal transplantation. Accumulation of urea, guanidino compounds, uric acid, hippuric acid, various amino acids, polypeptides, polyamines, phenols and conjugates of phenol, phenolic and indolic acids, acetone, glucuronic acid, carnitine, myoinositol, sulphates and phosphates has been reported in the literature (Enomoto et al., 2003; Topczewska-Brunns et al., 2002).

By some sources, uremic retention solutes are subdivided into three major classes: 1) small solutes (<500 Da) with no known protein binding; 2) solutes with known or likely protein binding and 3) middle molecules (≥ 500 Da). This classification is based on the characteristics that potentially influence their removal pattern during dialysis. Concentrations of 90 uremic solutes and ratios between mean uremic and normal concentration were reported by Vanholder et al. (2003a). Their meta-analysis illustrates the complexity of uremic retention. Not all solutes are retained to the same extent, and their retention is often not in correlation with the current markers, urea and creatinine. This is due to their molecular weight, protein binding, and/or multicompartmental behavior (Vanholder et al., 2001; Vanholder & De Smet, 1999). In addition, a high concentration is not necessarily related to a strong biologic activity. For example, the two molecules with the highest concentration (urea and creatinine) are known for their relatively limited biologic activity (Vanholder et al., 2001; Vanholder & De Smet, 1999). This indicates that removal strategies should be designed in such a way that not only the standard molecules, but also other molecules that might be important in the deterioration of the clinical condition, can be removed efficiently.

Urea has been used as a marker of uremic retention and removal for several years (Gotch & Sargent, 1985), and its removal is directly correlated with patient survival (Owen, Jr. et al., 1993). Nevertheless, there are very few studies demonstrating a direct biologic impact of urea at currently encountered uremic concentrations (Vanholder & De Smet, 1999), and those studies show an impact that not necessarily concentrates on key organic functions in the biochemical/biological status of the human body. When urea was added to the dialysate during a period of several months at concentrations largely exceeding those currently encountered in dialyzed uremics, uremic symptomatology was not consistently altered over the entire study period (Johnson et al., 1972), again suggesting that urea by itself is not very important in the development of uremic toxicity. It is difficult to explain the apparent paradox between the validity of urea as a marker and its presumed lack of toxicity. Of note, urea removal seems to be related as a surrogate marker only indirectly to survival, and not to quality of life. One possibility to consider is that urea removal by itself does not affect survival, but that it is representative for the removal of one or more other solutes with a more consistent impact. One such potential culprit is potassium, another small-water soluble compound known to substantially affect dialytic survival (Bleyer et al., 1999). Another possibility is that, together with urea, other uremic solutes antagonizing its toxic impact are retained (Lee et al., 1991). Finally, urea might be at the origin of other, more toxic moieties, such as some of the guanidines or carbamylation products (De Deyn et al., 2003; De Deyn et al., 2009; Stim et al., 1995; Vanholder & De Smet, 1999).

Other metabolic disturbances which may or may not be correlated with the intensity of cerebral dysfunction are acidosis, hyponatremia, hyperkalemia, hypocalcemia, hypermagnesemia, hyperhydration and dehydration (Bierman, 1970). However, the clinical features of uremic encephalopathy do not correlate precisely with any single laboratory change. On the other hand, symptoms are usually alleviated by dialysis and are generally relieved almost entirely after successful renal transplantation (Brenner et al., 1982; Raskin & Fishman, 1976; Teschan & Arieff, 1985).

4.2 Guanidino compounds

Among the guanidino compounds, guanidinosuccinic acid, methylguanidine, guanidine and creatinine were found to be highly increased in serum, cerebrospinal fluid and brain of

uremic patients (De Deyn et al., 2001). It is postulated that these compounds may contribute to the epileptic and cognitive symptoms accompanying uremic encephalopathy (D'Hooge et al., 1992b; D'Hooge et al., 1992a; Pan et al., 1996). Activation of the excitatory N-methyl-d-aspartate (NMDA) receptors and concomitant inhibition of inhibitory γ -aminobutyric acid (GABA)_A-ergic neurotransmission have been proposed as underlying mechanisms (De Deyn et al., 2001). This will be further explained in paragraphs 4.2.1 and 4.2.2.

In addition, transketolase is a thiamine-dependent enzyme of the pentose phosphate pathway that is found predominantly in the myelinated structures of the nervous system and has been reported to have a critical role in the maintenance of axon-cylinder myelin sheaths (Dreyfus, 1965; Yonezawa & Iwanami, 1966). This enzyme was shown to be significantly inhibited by plasma, cerebrospinal fluid and low molecular weight (<500 dalton) dialysate fractions obtained from patients with uremia (Sterzel et al., 1971). It is also of interest that in uremic subjects, transketolase activity of erythrocytes was found to be below normal but increasing following dialytic therapy. Guanidinosuccinic acid was capable of reproducing this inhibition which might underlie demyelinative changes contributing to both central and peripheral nervous system changes in chronic uremia (Lonergan et al., 1971). Moreover, other guanidino compounds, such as guanidine and methylguanidine, have been shown *in vivo*, in experimental animals, to induce clinical alterations comparable to those observed in uremia. Methylguanidine induced a syndrome similar to the uremic encephalopathy including epilepsy and symptoms similar to the uremic "twitch-convulsive" syndrome (Giovannetti et al., 1969; Matsumoto et al., 1976; Minot & Dodd, 1933; Mori, 1987). In decreasing potency, guanidinosuccinic acid, methylguanidine, guanidine and creatinine inhibited responses to GABA and glycine on mouse neurons in cell culture (De Deyn & Macdonald, 1990). The same order of epileptogenic potency was found for these uremic guanidino compounds in behavioral studies (D'Hooge et al., 1992b). Guanidinosuccinic acid brain concentrations in this chemical model of epilepsy were comparable to the levels observed in uremic brain (De Deyn et al., 1992a). The effects on inhibitory neurotransmission might, in combination with the other effects exerted by these toxins, underlie the pathogenesis of the myoclonus and epilepsy. Moreover, guanidinosuccinic acid was shown to inhibit excitatory synaptic transmission in CA1 region of rat hippocampal slices; this is an effect that might contribute to the cognitive symptomatology presenting in uremic encephalopathy (D'Hooge et al., 1991).

Guanidino compounds are produced as a result of protein and amino acid metabolism. Specific guanidino compounds were found to accumulate in biologic fluids and tissues of uremic patients. Their levels have been determined in serum, urine and cerebrospinal fluid of non-dialyzed and dialyzed renal insufficient patients. Four highly increased compounds are creatinine, guanidine, guanidinosuccinic acid and methylguanidine. In addition, accumulation of asymmetric (ADMA) and symmetric (SDMA) dimethylarginine was reported. In the case of guanidinosuccinic acid, increased cerebrospinal fluid concentrations of severely uremic patients were found to be as high as 350 times the mean concentration in controls.

In addition, guanidino compounds are found to stimulate leukocytes, with methylguanidine and guanidinoacetic acid significantly enhancing the lipopolysaccharide-stimulated production of tumor necrosis factor- α by normal monocytes (Glorieux et al., 2004) and SDMA enhancing the monocytic burst via store-operated calcium influx (Schepers et al., 2009). In addition, guanidino compounds also modify albumin structure in such way that

they decrease the protein binding of homocystein (Perna et al., 2004). The resulting free active homocysteine consequently contributes to cardiovascular damage.

Impaired cognition and epileptic symptomatology are the most typical manifestations of uremic encephalopathy. However, it is not entirely clear which of the putative uremic toxins are responsible for these central nervous system complications in uremia. Probably, the complications are due to the combined effects of different neurotoxic compounds. Guanidino compounds may play an important role in the etiology of uremic encephalopathy and they might contribute to the hyperexcitability of the uremic brain. A possible mechanism is described in the next paragraph.

4.2.1 Effects of uremic guanidino compounds on amino acid receptors

The four most increased uremic guanidino compounds induced clonic-tonic convulsions in adult mice (D'Hooge et al., 1992b). Guanidinosuccinic acid and methylguanidine were markedly more potent convulsants than guanidine and creatinine. Brain concentrations corresponding with the intraperitoneal CD50 (convulsive dose in 50%) of these convulsants were 1328 nmol/g tissue for creatinine, 209 nmol/g tissue for guanidine, 56 nmol/g tissue for guanidinosuccinic acid, and 94 nmol/g tissue for methylguanidine. Apparently, brain creatinine and guanidinosuccinic acid concentrations, corresponding with intraperitoneal doses that induce clonic convulsions in mice, are similar to the concentrations found in brain of uremic patients. However, creatinine only induced myoclonic jerking and slight convulsions, whereas guanidinosuccinic acid induced vigorous generalized clonic and tonic convulsions. The convulsive concentrations in mice of guanidine and methylguanidine were higher than those found in uremic brain. Guanidinosuccinic acid is highly increased in uremic serum, cerebrospinal fluid, and brain. This compound was shown by our group to be an experimental convulsant (D'Hooge et al., 1992b; D'Hooge et al., 1992a). In addition, it appears to be the uremic guanidino compound most likely to play an important role in the etiology of the hyperexcitability of uremic brain. The compound induced clonic and tonic convulsions as well as epileptiform electrocorticographic discharges in adult mice (D'Hooge et al., 1992a).

Neuroexcitatory effects of these compounds might be due to their actions at inhibitory and excitatory amino acid receptors. The four uremic guanidino compounds blocked GABA- and glycine-evoked depolarization in mouse spinal cord neurons in primary dissociated cell cultures (De Deyn & Macdonald, 1990). Guanidinosuccinic acid was shown to be the most potent compound, whereas methylguanidine, guanidine, and creatinine (in decreasing order) blocked GABA and glycine responses less potently. It was suggested that the uremic guanidino compounds might be blocking the GABA_A and glycine receptor-associated chloride channel (De Deyn et al., 1991). Later studies using the patch clamp technique suggested that guanidinosuccinic acid, methylguanidine, and creatinine may rather act as competitive antagonists at the transmitter recognition site of the GABA_A receptor (D'Hooge et al., 1999). Depending on the clamping potential, GABA-evoked outward or inward whole-cell currents, which were blocked by the GABA_A receptor antagonist bicuculline. Guanidinosuccinic acid, methylguanidine, and creatinine dose-dependently block these GABA-evoked whole-cell currents (D'Hooge et al., 1999). Guanidinosuccinic acid was shown to be more potent than methylguanidine or creatinine, but all three blocked inward as well as outward GABA-evoked current. The GABA_A and glycine receptor antagonism that was shown in *in vitro* experiments, might underlie the convulsive action of the uremic

guanidino compounds *in vivo* and might contribute to the epileptic symptomatology in uremia. However, in the case of guanidinosuccinic acid induced clonic convulsions, antiepileptic drugs like diazepam or phenobarbital did not or only slightly attenuate these convulsions (D'Hooge et al., 1992a; D'Hooge et al., 1993). Competitive and noncompetitive NMDA receptor antagonists, on the other hand, did effectively block these convulsions (D'Hooge et al., 1993). Also, guanidinosuccinic acid potentiated NMDA- but not glutamate- or kainate- induced convulsions. These findings suggested that, in addition to the blockade of GABAergic inhibition, NMDA receptors were somehow involved in the guanidinosuccinic acid induced convulsions. The hypothetical activation of NMDA receptor by guanidinosuccinic acid was first corroborated by Reynolds and Rothermund (Reynolds & Rothermund, 1992). They found that creatinine, guanidine and methylguanidine blocked the NMDA receptor-associated ionophore in a similar manner to magnesium, but that guanidinosuccinic acid was able to enhance [³H]dizocilpine binding to rat brain membranes, and increase intracellular [Ca²⁺] in rat forebrain neurons. Both latter effects are indicative of agonist actions of guanidinosuccinic acid at the NMDA receptor. We found behavioral and electrophysiological evidence that guanidinosuccinic acid (but not methylguanidine) acts as a selective agonist at NMDA-type excitatory amino acid receptors in a similar manner to the structurally related L-aspartate (D'Hooge et al., 1996). Guanidinosuccinic acid was shown to abolish the excitatory postsynaptic potential recorded from CA1 region in rat hippocampal slices (D'Hooge et al., 1991; D'Hooge et al., 1996). The inhibition of this effect by a selective NMDA receptor antagonist indicated that this was probably due to NMDA receptor-mediated depolarization of hippocampal neurons (D'Hooge et al., 1996). Pan et al. (Pan et al., 1996) demonstrated that intrahippocampal injection of guanidinosuccinic acid in rats induces epileptiform electrographic discharges, and leads to hippocampal damage, which could be blocked by treatment with the NMDA receptor antagonist ketamine. It is indeed well established that the application of NMDA agonists, even in amounts that are not immediately toxic, induce neurodegeneration. Excessive calcium influx through NMDA receptor-associated ion channels leads to loss of mitochondrial and nuclear function, activation of proteases and other calcium-dependent enzymes, and ultimate excitotoxic cell death. The effect of intrahippocampal guanidinosuccinic acid injection on both (cognitive) behavior and hippocampal volume in mice was investigated as well (Torremans et al., 2005). A significant dose-dependent effect of intrahippocampal injection of guanidinosuccinic acid on cognitive performance, activity, and social exploratory behavior was observed. Volume of hippocampal cornu ammonis region decreased significantly and dose-dependently after guanidinosuccinic acid injection. Systemic guanidinosuccinic acid injection increased cGMP concentration in hippocampal formation. Knowledge of neurotoxic effects and mechanisms of action of guanidinosuccinic acid and other uremic retention solutes could help in the development of more efficient treatment of uremic patients.

4.2.2 Hypothetical mechanism of neuroexcitation by uremic guanidino compounds

Based on the results summarized above, a hypothetical mechanism for the action of uremic guanidino compounds on glutamatergic transmission in the central nervous system was proposed by De Deyn et al. (De Deyn et al., 2009) (Fig. 2). A simplified model of the Schaffer collateral-pyramidal cell synapse in the CA1 region of the rodent hippocampus was used (Collingridge & Lester, 1989). In a changed form, the proposed mechanism might also apply to other glutamatergic pathways. The mechanism could explain the neuroexcitatory and

convulsant actions of guanidinosuccinic acid (and other uremic guanidino compounds) in experimental animals, but it might also link uremic guanidino compounds to uremia-associated epileptic symptomatology. In CA1 region, fast synaptic events are carried by two kinds of ionotropic excitatory amino acid receptors: α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) and NMDA receptors (Collingridge & Lester, 1989). Both receptor types react to endogenously released L-glutamate. During low-frequency transmission, the NMDA receptor-associated ionic channel is voltage dependently blocked by Mg^{2+} . Low-frequency activation of AMPA receptors does elicit Na^+ influx, but this depolarizing current does not provide sufficient membrane depolarization to reduce the Mg^{2+} block on the NMDA receptor. GABAergic interneurons mediate powerful feedforward as well as feedback synaptic inhibition. Endogenously released GABA binds to $GABA_A$ receptors, activating the ligand-gated ionic channel of the receptor, and eliciting hyperpolarizing chloride influx.

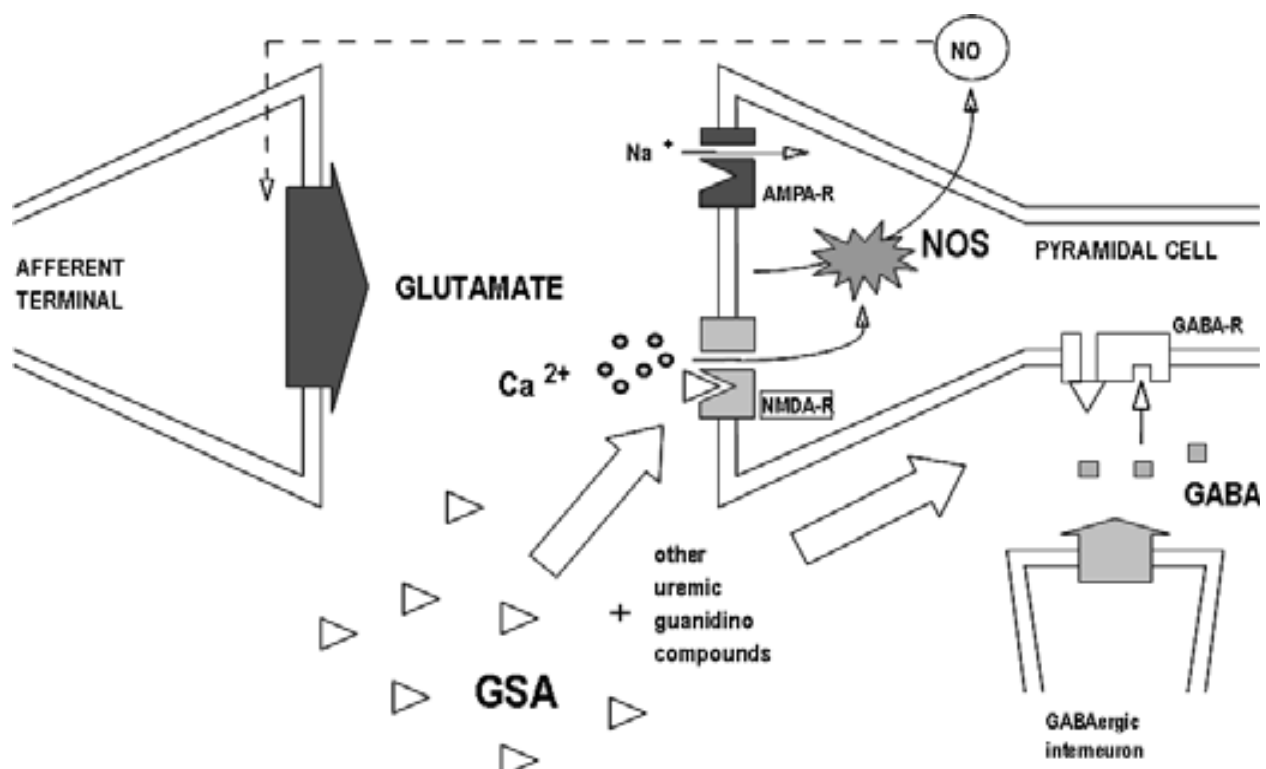


Fig. 2. Excitatory effects of uremic guanidino compounds. Hypothetical mechanism of action of guanidinosuccinic acid on synaptic transmission in rat hippocampal CA1 region. During low-frequency transmission, the excitatory neurotransmitter L-glutamate is released by the afferent terminal and binds to AMPA and NMDA receptors (NMDA-R). GABAergic interneurons provide synaptic inhibition through activation of $GABA_A$ receptors ($GABA-R$) and chloride influx. Due to insufficient membrane depolarization, the voltage dependent Mg^{2+} block on the NMDA-R is not lifted. However, in the presence of increased guanidinosuccinic acid levels, blocked $GABA_A$ receptors, and depolarizing effects of other uremic guanidino compounds, the Mg^{2+} block may be lifted from the NMDA-R. Activation of NMDA-Rs elicits Ca^{2+} influx through NMDA-R ionophores and activation of Ca^{2+} -triggered events such as activation of nitric oxide synthase (NOS) leading to nitric oxide (NO) production and increased glutamate release presynaptically (De Deyn et al., 2009).

According to the proposed mechanism (Fig. 2), guanidinosuccinic acid evokes activation of NMDA receptors in conjunction with blockade of GABA_A receptor ionophores. Under these conditions, the pyramidal cells might be sufficiently depolarized to reduce the Mg²⁺ block on NMDA receptors. Activation of NMDA receptors elicits Ca²⁺ influx, potentially causing calcium-mediated neurotoxicity. Production of nitric oxide through calcium dependent activation of nitric oxide synthase could be one of the mechanisms involved in the sustained excitatory activity following guanidinosuccinic acid application. As already mentioned, Pan et al. (Pan et al., 1996) have shown NMDA receptor-mediated hippocampal damage following intrahippocampal injection of guanidinosuccinic acid in rats. In uremic brain, the depolarizing effects of guanidino compounds and other uremic toxins might enhance the effect of guanidinosuccinic acid. The joint presence of increased levels of uremic guanidino compounds could increase the block on GABA_A receptors since it has been shown that, e.g., co-application of guanidine and methylguanidine results in a significantly larger inhibition of GABA responses than when either of these guanidino compounds were applied alone (De Deyn & Macdonald, 1990). Moreover, guanidino compounds were shown to have other neurotoxic effects, which might also lead to neuronal depolarization (Mori, 1987). One such effect is the inhibition of brain Na⁺/K⁺-ATPase by methylguanidine (Yokoi et al., 1984).

4.3 Energy metabolism

Besides toxins, evidence indicates that energy metabolism might play a role. Experimental animal studies and *in vitro* tests demonstrated disturbances of intermediary metabolism. In the brain of rats with acute renal failure, creatine phosphate, adenosine triphosphate and glucose levels are increased in the presence of decreased adenosine monophosphate, adenosine diphosphate and lactate levels. Thus, the uremic brain in experimental uremia appears to use less adenosine triphosphate and to produce less adenosine diphosphate, adenosine monophosphate and lactate. These changes are associated with a decrease in both brain metabolic rate and cerebral oxygen consumption (Mahoney et al., 1984; Van den Noort et al., 1968) and are consistent with a generalized decrease in brain energy use. Moreover, an inhibition of cerebral sodium-potassium-ATPase was shown in experimental uremic animals (Burn & Bates, 1998; Minkoff et al., 1972). This could correlate with the elevation in intracellular sodium and could therefore be associated with some of the aspects of cerebral dysfunction, particularly with seizure activity. More recent studies on metabolically active and purified brain synaptosomes showed that both the sodium potassium adenosine triphosphate pump and several calcium pumps are altered in uremic rats (Fraser et al., 1985a; Fraser et al., 1985b).

4.4 Hormonal disturbances

The role of hormonal disturbances in the genesis of the uremic syndrome should be considered as well. Blood levels of many hormones such as parathyroid hormone, insulin, growth hormone, glucagon, thyrotropin, prolactin, luteinizing hormone and gastrin are elevated in patients with uremia. One of the major hormonal imbalances in uremia is the rise in the levels of parathyroid hormone. The possible pathophysiological role of parathyroid hormone in the development of nervous system complications in uremia has been considerably discussed (Heath et al., 1980; Slatopolsky et al., 1980). Parathyroid hormone appears to produce some of the central nervous system changes of uremia in

healthy dogs (Guisado et al., 1975). Previously parathyroidectomised rats, subjected to bilateral uretral ligation, were protected against the uremia-induced alterations of somatosensory evoked potentials (Kanda et al., 1990). In humans, parathyroid hormone produced central nervous system effects, even in the absence of renal failure (Cogan et al., 1978). The mechanisms by which parathyroid hormone might impair central nervous system function are not completely understood. However, the increased calcium content in diverse tissues, among which brain, in patients with uremia and secondary hyperparathyroidism suggests that parathyroid hormone may somehow facilitate the entry of calcium in these tissues (Akmal et al., 1984; Burn & Bates, 1998; Massry, 1985). Since calcium is an essential mediator of neurotransmitter release and plays an important role in intracellular metabolic and enzymatic processes, alterations of brain calcium, may possibly disrupt cerebral function by interfering with any of these processes (Rasmussen, 1986).

Brain edema and alterations in water transport have also been implicated (Arieff et al., 1973; Arieff & Massry, 1974). Decreased brain energy demand, free amino acid changes, and blood-brain barrier derangement have been shown to be involved in both acute and chronic uremic encephalopathy (Jeppsson et al., 1982; Kikuchi et al., 1983; Mahoney et al., 1984). In a mouse model for acute kidney injury, it was demonstrated that pyknotic neuronal cells were significantly increased in region CA1 of the hippocampus. In addition, acute kidney injury resulted in significant increases in levels of the chemokines keratinocyte-derived chemoattractant and G-CSF in the brain at 24h after ischemia. On the other hand, brain water content during acute kidney injury was not increased or even decreased, while an increase in microvascular permeability in the brain was observed (Liu et al., 2008).

5. Treatment

5.1 Dialytic treatment

Acute uremic encephalopathy reverses with hemodialysis or peritoneal dialysis, although a lag time of 1 to 2 days is usually required before mental status clears. Subtle cognitive difficulties may persist even after dialysis. A disadvantage of dialysis is its non-specificity and the fact that it removes also essential compounds. In addition, lipophilic compounds, which may be responsible at least in part for functional alterations in uremia, are inadequately removed by dialysis. Also, renal transplant can be considered a treatment. However, uremic encephalopathy can complicate renal transplant.

5.2 Non-dialytic treatment

Removal of uremic toxins are also influenced by intestinal intake and preservation of the renal function. Intestinal uptake can be reduced by influencing dietary uptake or by oral administration of absorbents. Approaches that have been shown to result in decrease in concentration include a low protein diet, administration of prebiotics such as resistant starch (Birkett, 1996) or probiotics such as bifidobacterium (Taki, 2005). Preservation of residual renal function may also be an important manner to pursue additional removal of retention solutes.

Acute renal failure induces brain mitochondrial dysfunction. Administration of the antioxidants N-acetylcysteine and deferoxamine was able to prevent the inhibition of

mitochondrial respiratory chain complexes I and IV (Barbosa et al., 2010). Therefore, it can be speculated that excessive reactive species generation might contribute to the neuropathology associated with acute renal failure. Creatine kinase was inhibited in prefrontal cortex, cerebral cortex and hippocampus in an animal model of acute renal failure. In this way, diminished creatine kinase might be involved in the cognitive impairment in patients with uremic encephalopathy. The inhibition of creatine kinase was prevented by antioxidants. It was speculated that oxidative stress might be involved in the mechanism of creatine kinase activity inhibition (Di-Pietro et al., 2008). In addition, increased malondialdehyde and diminished glutathione levels in brain of rats submitted to a model of chronic renal failure (Sener et al., 2007).

6. Dialysis disequilibrium

Dialysis disequilibrium syndrome occurs in patients receiving hemodialysis. The symptoms include headache, nausea, emesis, blurred vision, muscular twitching, disorientation, delirium, hypertension, tremors and seizures. The condition tends to be self-limited and subsides over several hours. It is attributed to a reverse urea effect. Urea is cleared more slowly from the brain than from the blood, an effect that causes an osmotic gradient leading to the net flow into the brain and to transient cerebral edema (Bucurescu, 2008).

7. Dialysis encephalopathy

Some patients undergoing long-term dialysis develop dialysis encephalopathy or dialysis dementia. This is a subacute, progressive and often fatal disease. It is believed to be a part of a multiple system disease that includes encephalopathy, osteomalacic bone disease, proximal myopathy and anemia. Other symptoms include dysarthria, apraxia, personality changes, psychosis, myoclonus, seizures and finally dementia. In most cases, the condition progress to death in six months (Brouns, 2004).

8. Conclusion

In spite of the introduction of different dialytic procedures during the last decades, the neurological complications of uremia, although declined, remain manifold and sometimes serious. Although onset of uremic encephalopathy is often insidious, early recognition is very important as it comes to treatment. The different symptoms to be looked for are reviewed in this chapter. Urea is often used as a marker of dialytic efficiency, but has limited biological activity. Therefore, in the future, removal strategies should be designed in such a way that not only the standard molecules, but also other molecules that might be important in the deterioration of the clinical condition, can be removed efficiently. In contrast, the guanidino compounds are of great biological relevance. Those molecules have been shown to have neuroexcitatory effects and lead to convulsions. Activation of the excitatory N-methyl-d-aspartate (NMDA) receptors and concomitant inhibition of inhibitory γ -aminobutyric acid (GABA)_A-ergic neurotransmission have been proposed as underlying mechanisms. In this chapter, putative action mechanisms are enlightened but those pathways remain to be corroborated. Knowledge of neurotoxic effects and mechanisms of action of guanidinosuccinic acid and other uremic retention solutes could add to the limited treatment options of uremic patients.

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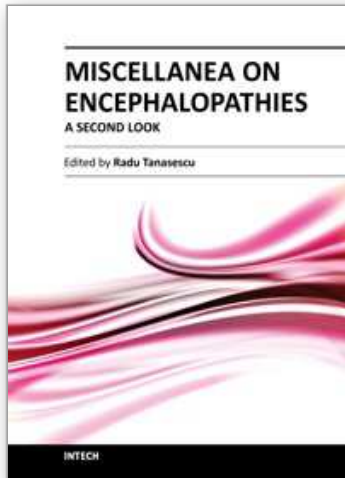
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