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## The Use of Microdialysis in the Study of Encephalopathies

Liliana Carmona-Aparicio, Liliana Rivera-Espinosa  
and Hugo Juárez-Olguín  
*Instituto Nacional de Pediatría  
México, D.F.*

### 1. Introduction

Microdialysis is a technique that was devised by Bito *et al.* (1966) in a study to determine free aminoacids and electrolytes in cerebrospinal fluid and blood plasma in dogs. It consists of recollection of samples in specific places by using semi-permeable membranes, used to evaluate compounds (endogenous neurotransmitters or exogenous such as drugs), in extracellular spaces from different tissues as brain, skin, subcutaneous, tumors, kidney, abdominal and femoral adipose tissue, muscle, lung, middle ear fluid, and other extracellular spaces like blood. Currently, one of the main applications of this methodology in the field of neuroscience is to conduct studies to monitor the release of different substances in brain of conscious and unconscious anesthetized animals. The technique has also been used in surgical procedures as well as in monitoring patients in intensive care unit with traumatic brain injury and subarachnoid hemorrhage. It is employed in neuronal diseases like Epilepsy, Alzheimer, Parkinson, Huntington, Amyotrophic Lateral Sclerosis (ALS) and Encephalopathies.

Encephalopathies are a group of diseases affecting brain which are attributed to a wide range of etiologies with spectra of symptomatology. The main causes of encephalopathy are infections, liver damage, anoxia, hypoxia, ischemia, and kidney failure. This pathology can undergo through altered mental state. The mental alteration may be subtle with slow development lasting for years or it may be profoundly obvious with fast development. The cardinal symptoms of this state consist of inattentiveness, poor judgment, or poor motor coordination, lethargy, dementia, seizures, tremors, muscle twitching and coma. The severity and type of symptoms are related to the level of severity and the cause of the brain disease or damage. The diagnosis of encephalopathy is done by clinical tests during the physical memory and coordination tests, and it is made when the altered mental state is accompanied by another primary diagnosis such as chronic liver disease, kidney failure, anoxia, or others. Thus, the complications derived from encephalopathies arise from a primary health problem or a previous primary diagnosis. The need to avoid complications caused by late diagnosis resides on identification and clarification of the mechanisms underlying the neuronal damage and a search for markers that would give rise to timely diagnosis of the pathology. As a consequence, researchers in neurosciences have devoted their time in resolving this issue through various experimental approaches including

microdialysis. Currently, microdialysis is not only used to determine the neurochemical abnormalities induced by encephalopathy, but also in the determination of the therapeutic effects of various drugs in the treatment of this pathologic condition. In this chapter we will discuss the utility of microdialysis as a tool for the study of encephalopathy in human and experimental models.

## 2. Microdialysis technique

### 2.1 General characteristics

Microdialysis was developed for continuous sample collection in specific brain areas. This procedure permits the exploration, in real time, of the chemical interchange among cells in extracellular space using samples from the extracellular fluid. This is contrary to other sampling schemes like blood sampling which does not reflect specific changes for the mere fact that molecules are diluted into a relatively high compartment that irrigate vats tissues. It also provides information without the need of dissecting tissue samples to gather information that would be a picture of biochemical events (Robinson & Justice, 1991).

The group of Bito *et al* (1966) was the first to introduce "bags of dialysis" within the subcutaneous tissue of the neck and within the parenchyma in the cerebral hemisphere of dogs in order to analyze the content of amino acids in this brain region. These experiments introduced the idea of a "compartment" surrounded by a dialyzing membrane balanced with the extracellular space (Robinson & Justice, 1991).

Microdialysis is an experimental method consisting of a closed system, in which a thin tube with a dialyzing membrane is inserted into a particular region of the brain or parenchyma of some other tissues like kidney, skin or others where the cannula is fixed. The principle of microdialysis is based on the physicochemical phenomenon of passive diffusion, that occurs when a substance is not homogeneously distributed in an environment accumulating a force that tend to equalize the chemical potential of the same throughout the space, thereby producing a molecular flow from the higher chemical potential of this substance to the lower concentration compartment (Bellander *et al.*, 2004; Di Chiara *et al.*, 1996; Hsiao *et al.*, 1990; Kendrick *et al.*, 1988; Kennth *et al.*, 2002; Juhasz *et al.*, 1989).

It is a spontaneous and irreversible process in which there is an expansion of a substance in solution as a result of movement of its particles, to fill all available volume in which they are found. This movement is constant and random molecules can interchangeably move from one direction to another. However, if one takes into account that the number of particles of a given substance is higher in places of higher concentrations, there is a predominant shift to low concentration sites, giving rise to a net diffusion of the substance from the sites of higher concentration to lower concentration. It is worth mentioning that semi-permeable membranes are characterized by pore size, only found in low weight molecules. This principle is schematized in Figure 1 (Hocht, 2007; Hsiao *et al.*, 1990; Jaitovich, 2003; Juhasz *et al.*, 1989; Orłowska-Majdak, 2004; Verbeeck, 2000; Ungerstedt & Hallström, 1987).

Microdialysis involves the passage of a vehicle (perfusion) at continuous and defined flow through a membrane, which is implanted in the tissue of interest in case of *in vivo* experimental models (Figure 2), and in humans, in a solution of known concentration in

case of *in vitro* experiments. The choice of vehicle in this type of experimentation must be adequate for the environment where the cannula of microdialysis is fixed. Aqueous solutions are commonly used with concentrations of sodium and potassium ions in low concentrations, without the presence of proteins or at very low concentrations that resemble the extracellular space to study. In some cases, the vehicle may contain proteins to prevent drug sticking to the sides of the cannula (Boschi & Scherrmann, 2000; Elmquist & Sawchuk, 1997; Orłowska-Majdak, 2004; Plock & Kloft, 2005; Verbeeck, 2000).

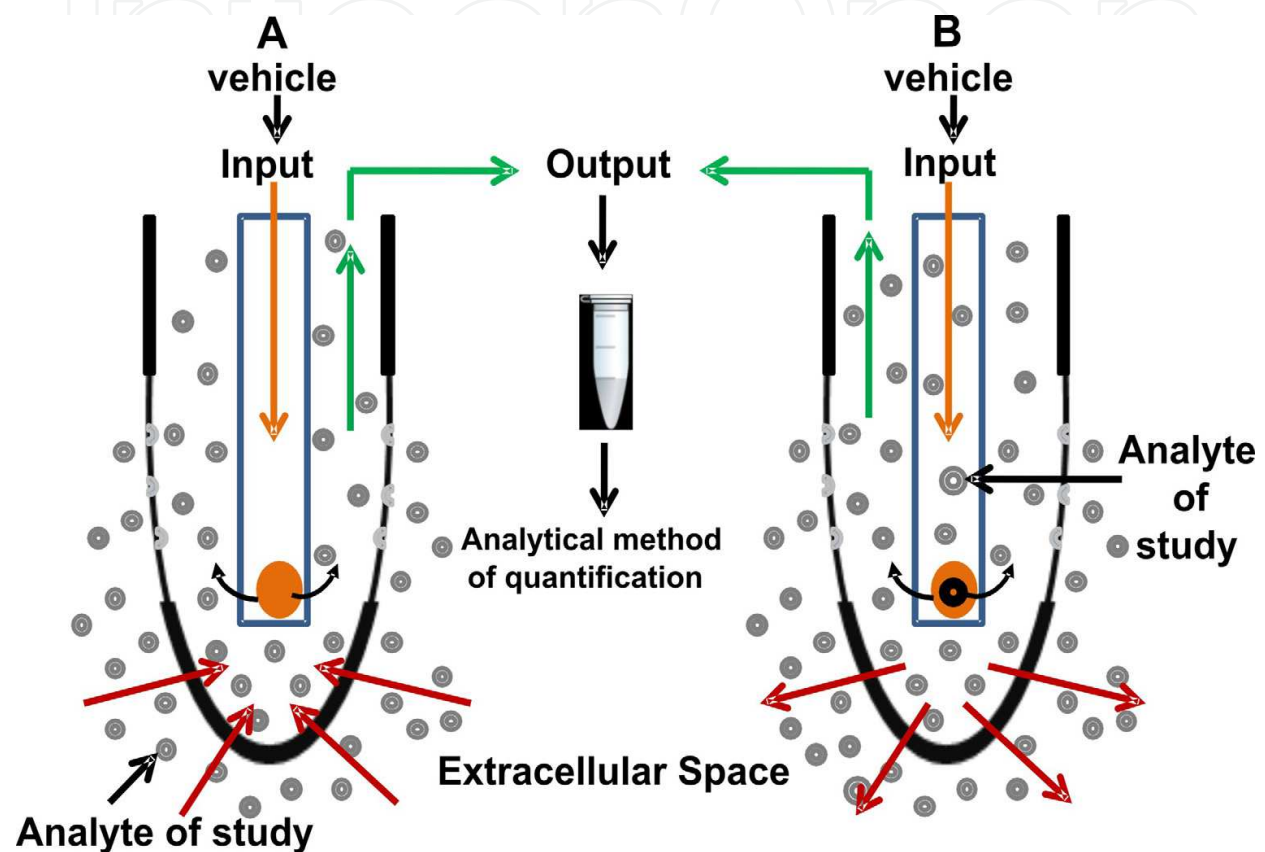


Fig. 1. Directions of molecular migration through dialyzing membrane during microdialysis (A) and retrodialysis (B). The analyte of study in (A) is from extracellular space whereas that in (B) is from external vehicle. Note that the test substance and the case of microdialysis or retrodialysis do not exceed the size of the pores present in the semipermeable membrane. The inlet and outlet terms refer to the vehicle entry and exit respectively. The outlet is always connected to a storage container subsequently quantified by the analytical method with increased sensitivity to the analyte under study.

Vehicles used in microdialysis are of different chemical composition, such as saline, ringer buffers, and artificial cerebrospinal liquid. In the case of retrodialysis, the vehicle is the matrix in which interest analyte is expected to exert a physiological and biochemical effects in the extracellular space of interest. In the process of infusion, the vehicle flow is generated by the movement of analyte that is released by forming a concentration gradient between the two regions separated by a membrane (Figure 3).

The extracellular fluid from the site of membrane location dictates the composition of the infused fluid used in *in vivo* paradigms. Dissemination occurs through a semipermeable



membrane. Endogenous compounds such as neurotransmitters, neuropeptides, neurohormones, etc. and exogenous compounds (drugs and metabolites) spread to the interior, while compounds that have been added diffuse out of the vehicle of the retrodialyzer infusion solution (Figure 1).

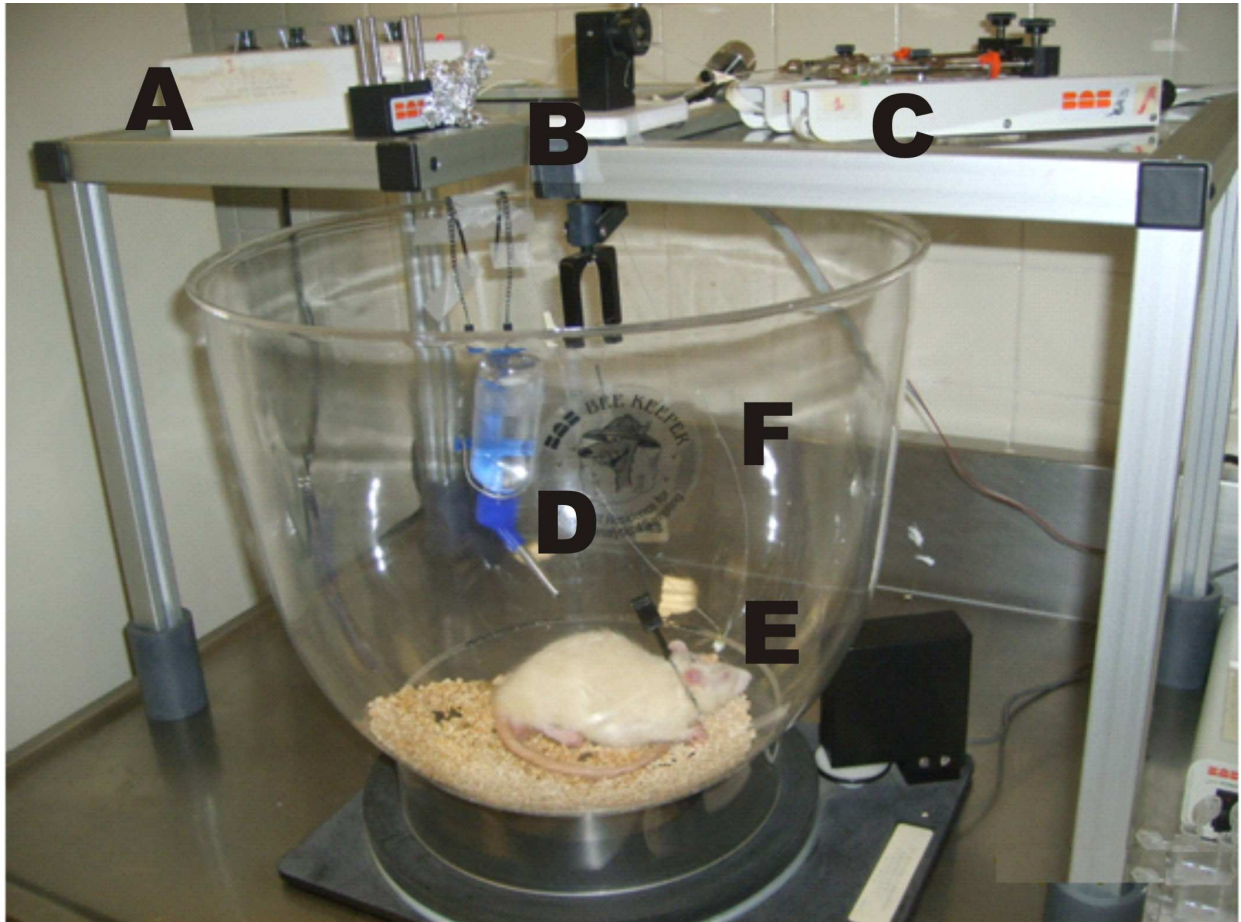


Fig. 2. Representative image of microdialysis system for experimental models *in vivo*.

A) Velocity controller, B) flow manager, C) booster pump, D) inlet tube, E) clamping collar, and F) Outlet tube.

Several factors affect this diffusion process in the semipermeable membrane of the cannula of microdialysis, and consequently the recovery of the substance of interest. These factors are: a) The flow rate, where the recovery is inversely proportional to the infusion rate and the recovery of the substance of interest is close to one hundred percent when the flow is near zero and it is minimum when it is fast; b) the membranes composition: There are over 30 different materials for the production of membranes which can be directly derived from natural products, semi-synthetic and fully synthetic; c) the presence of surface charges that reduce the recovery of certain charged molecules, which does not happen with neutral molecules; d) total membrane area (length), where recovery is directly proportional to the total area of the membrane, and e) temperature of the system, where 37 °C facilitates the diffusion process.

## 2.2 Advantages and disadvantages

The microdialysis technique has a number of advantages and limitations over other similar techniques such as push-pull cannula. The principal advantages are: a) easy to set up in working routine; b) facilitates the manufacture of probes with homogeneous characteristics; c) can be attached to different systems for chemical analysis; d) systemic or local administration of substances can be easily done; e) stimulation and recording electrical activity can be coupled to microdialyzer system; and f) monitoring abnormal behavior in animals in free movement. The principal disadvantages are: a) it is an invasive technique that generates tissue damage and gliosis, b) it presents low recovery rates of high molecular weight molecules; and d) the final volume presents analytical limitations (Bonate, 1995; Dash *et al.*, 1999; Johnston & Gupta, 2002; Mendelowitsch, 2001; Orłowska-Majdak, 2004; Parent *et al.*, 2001; Viñas, 2001).

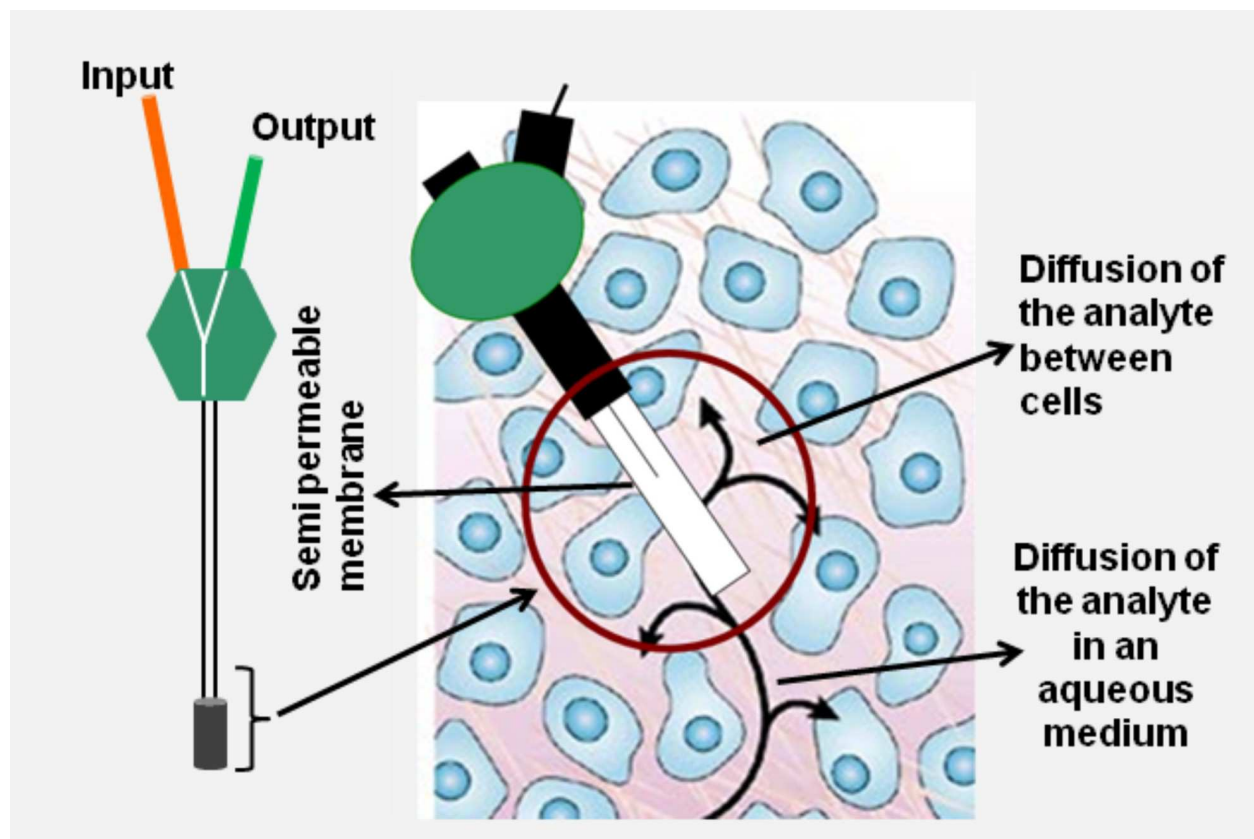


Fig. 3. Schematic representation of the microdialysis cannula place in an *in vivo* study. The microdialysis cannula membrane highlighted is the active part. The scheme shows the localization of the active part of microdialysis cannula between the extracellular space of the cells.

One of the principal disadvantages of microdialysis technique is that it does not ensure complete recovery of the substances present in the extracellular space, or externally administered to the space for quantification. This depends on different factors such as the type of membrane, the molecular weight of substances, their permeability through the membrane, and the rate of vehicle flow. The amount of substances crossing the membrane under certain experimental conditions is defined as the recovery percent and it is the result

of the relationship between the concentrations of the substance measured in the collected sample and their concentration in the outer membrane of microdialysis. This recovery is usually determined *in-vitro* and expressed as a percentage. The recovery of different probes is calculated for each of the studied substances. The probes are placed in dissolution with known concentration.

The recovery of the substance across the probe is determined by calculating the percentage of the measured amounts in dialysis with respect to the total amount present in the external environment of the probe. For this reason, it is very important to determine the best experimental condition (Boschi & Schermann, 2000; Dash *et al.*, 1999; Hitzman *et al.*, 2005).

This mathematical relationship is expressed in the formula below:

$$\text{Relative recovery (RR): } RR = 1 - (C_{\text{out}} / C_{\text{in}})$$

Where “C in” is the analyte concentration in the perfusate, and “C out” is the analyte concentration in the dialysate.

### 3. General characteristics of encephalopathies

Encephalopathy is a series of pathological conditions affecting the brain. This includes but not limited to the cerebral cortex intracranial white matter, basal ganglia, hypothalamus, brainstem, and cerebellum (Cash *et al.*, 2010). Encephalopathy is a term that means brain disease, damage, or malfunction and this may present a very broad spectra of symptoms that range from mild, such as memory loss or subtle personality changes, to severe, such as dementia, seizures, coma, or death. In general, encephalopathy is manifested by an altered mental state that is sometimes accompanied by physical manifestations, for example, poor coordination of limb movements (Müller *et al.*, 2008). The term "encephalopathy" is very broad and in most cases, is preceded by various terms that describe the reason, cause, or special conditions of the patient that leads to brain malfunction (Goetz *et al.*, 1999). For example, anoxic encephalopathy means brain damage due to lack of oxygen, and hepatic encephalopathy means brain malfunction due to liver disease. Additionally, some other terms may either describe body conditions or syndromes leading to a specific set of brain malfunctions. Examples of these are metabolic encephalopathy and Wernicke's encephalopathy (Wernicke's syndrome). There are over 150 different terms that modify or precede "encephalopathy" in the medical literature (Randolph *et al.*, 2009).

#### 3.1 Causes

The causes of encephalopathy are both numerous and varied. Some examples include: infections (bacteria, viruses, parasites), anoxia (lack of oxygen in the brain), alcohol consumption, liver failure, kidney failure, metabolic diseases, brain tumors, many types of toxic chemicals, alterations in brain pressure, and poor nutrition (Hillbom & Marttila, 2010). These examples do not cover all the potential causes of encephalopathy but are listed to demonstrate the wide range of causes (Sato & Moriuchi, 2010). Although numerous causes of encephalopathy are known, the majority of cases are categorized into: infection, liver damage, anoxia, and kidney failure (Chung & Podolsky, 2005).



### 3.2 Symptoms

Despite the numerous and varied causes of encephalopathy, at least there is a symptom common to all cases: an altered mental state. The altered mental state may be subtle with slow development during many years (for example, in hepatitis with decreased ability to draw simple designs, termed apraxia). On the other hand, it can be profoundly obvious and develop rapidly (for example, brain anoxia leading to coma or death in a few minutes). Often, symptoms of altered mental status can present as inattentiveness, poor judgment, or poor coordination of movements. Other symptoms that may occur include: lethargy, dementia, seizures, tremors, muscle twitching, and coma. Often, the severity and type of symptoms are related to the severity and the cause of the brain disease or damage. For example, alcohol-induced liver damage (alcoholic cirrhosis) can result in involuntary hand tremors (asterixis), while severe anoxia (lack of oxygen) may result in coma with no movement.

### 3.3 Diagnosis

The diagnosis of encephalopathy is usually by clinical tests done during the physical examination (mental status tests, memory tests, coordination tests) that document an altered mental state. With most cases, findings on clinical tests can either give definitive diagnosis or presumptive diagnosis of encephalopathy (Prakash & Mullen, 2010). Usually, the diagnosis occurs when the altered mental state is found in conjunction with a primary cause such as chronic liver disease, kidney failure, anoxia, or many other diagnoses. This is contrary to other sampling schemes like blood sampling which does not reflect specific changes for the mere fact that molecules are diluted into a relatively high compartment that irrigate vats tissues. Consequently, physicians may use several different tests at the same time to diagnose both the primary condition (the cause of encephalopathy) and the encephalopathy itself. This approach to diagnosis is common to most physicians, because many doctors view encephalopathy as a secondary complication of a primary underlying health problem.

The most frequently used tests are listed below and with some of the major primary causes, the tests may help in the diagnosis of: a) complete blood count or CBC (infections, loss of blood); b) blood pressure (high or low blood pressure); c) metabolic tests (blood levels of electrolytes, glucose, lactate, ammonia, oxygen, and liver enzyme levels); d) drugs or toxin levels (alcohol, cocaine, amphetamines, and many others); e) blood and body fluid cultures and analysis (infections of many types); f) creatinine (kidney function); g) CT and MRI scans (brain swelling, anatomical abnormalities, infections); h) abnormal blood flow to tissues and abscesses; i) Encephalogram or EEG (brain damage, abnormal brain wave patterns); and j) auto-antibody analysis (dementia caused by antibodies that destroy neurons). This list is not exhaustive, and not all the above tests are needed to reach a diagnosis. Normally, specific tests are usually ordered by the treating physician depending on the symptoms and history of the patient.

There are other Diagnostic Criteria of Encephalopathy. The most relevant are: a) gradual onset (in hours); b) progression in untreated patients; c) gradual decrease in the level of consciousness; d) patients treated with various CNS depressant medications; e) patients with any organ failure, postoperative electrolyte imbalance, endocrine diseases; f) no



evidence of brain tumor or stroke, but usually no focal hypoglycemia; g) sometimes preceded by focal or generalized seizures; h) increased spontaneous motor activity (asterixis, myoclonus, rigidity, etc.); i) changes in plasma biochemistry, and hemogram GSA; j) usually normal in imaging studies; k) generalized EEG abnormalities (slowing, triphasic waves); and l) gradual recovery to begin treatment (Randolph *et al.*, 1998).

### 3.4 Treatment

Treatment of encephalopathy varies depending on the primary cause of the symptoms. Consequently, not all cases of encephalopathy are treated in the same way. The best treatments are designed by the treating physician once the patient's primary diagnosis is made. Treatments are highly variable because the causes are so different (Bajaj, 2010). Examples can show how different "encephalopathy treatment" may change depending on the cause: a) short-term anoxia (usually less than two minutes): oxygen therapy; b) long-term anoxia: rehabilitation; c) short-term alcohol toxicity: IV fluids or no therapy; d) long-term alcohol status (cirrhosis or chronic liver failure): oral lactulose, low-protein diet, antibiotics; e) uremic encephalopathy (due to kidney failure): correct the underlying physiological cause, dialysis, kidney transplant; f) diabetic encephalopathy: glucose for hypoglycemia, removal of blood glucose to treat hyperglycemia; g) hypo- or hypertensive encephalopathy: raise (for hypotension) or reduce (for hypertension) blood pressure (Sundaram & Shaikh, 2009).

The key to treatment of any encephalopathy is to understand the basic cause and thus design a treatment scheme to reduce or eliminate the cause(s). Static encephalopathy (an altered mental state or brain damage that is permanent) is one type of encephalopathy difficult or impossible to treat. The best that can be done in this case if possible is to prevent further damage and implement rehabilitation to allow the individual to live at his or her highest possible functional level (Bismuth *et al.*, 2011).

### 3.5 Complications

Complications of encephalopathy vary from none to profound mental impairments that could lead to death. The complications can be similar in some cases. Also, many investigators consider encephalopathy to be a complication that arises from a primary health problem or primary diagnosis. Complications depend on the primary cause of encephalopathy and can be illustrated by citing a few examples from the wide variety of causes: a) hepatic (liver) encephalopathy (brain swelling with herniation, coma, death); b) metabolic encephalopathy (irritability, lethargy, depression, tremors; occasionally coma or death); c) anoxic encephalopathy (wide range of complications, from none in short-term anoxia to personality changes, severe brain damage and death in long-term anoxic events); d) uremic encephalopathy (lethargy, hallucinations, stupor, muscle twitching, seizures, and death); e) Hashimoto's encephalopathy (confusion, heat intolerance, and dementia); f) Wernicke's encephalopathy (mental confusion, memory loss, and decreased ability for eye movement); g) bovine spongiform encephalopathy or "Mad Cow disease" (ataxia, dementia and myoclonus or muscle twitching without any rhythm or pattern); h) Shigella encephalopathy (headache, stiff neck, delirium, seizures, coma); i) infectious causes of pediatric encephalopathy (irritability, poor feeding, hypotonia or floppy baby syndrome, seizures, death; Nabbout *et al.*, 2011).

The best way to understand potential complications is to discuss them with the diagnosing doctor who can explain the possible problems associated with the specific cause(s) of the type of encephalopathy (Sima, 2010).

### 3.6 Prognosis

The prognosis of a patient with encephalopathy depends on the initial cause and, in general, the length of time it takes to reverse, stop, or inhibit those causes. Consequently, the prognosis varies from patient to patient and ranges from complete recovery to a poor prognosis that often leads to permanent brain damage or death. One good example of this highly variable prognosis is a patient with hypoglycemic encephalopathy.

When patients with hypoglycemia are given glucose at first signs of encephalopathy (for example, irritability, mild confusion), most of them completely recover from the problem. Delays in correcting hypoglycemia (hours to days) may lead to seizures or coma which may be halted by treatment with complete or partial recovery (minimal permanent brain damage). A long delay or multiple delays in treatment can lead to a poor prognosis with extensive brain damage, coma, or death (Munoz, 2008).

Although the symptoms and time frame vary widely from patient to patient and according to the initial causes of encephalopathy (see above), the prognosis of each case usually follows the pattern described in hypoglycemic cause and depends upon the extent and rapidity with which the underlying cause is treated. The doctor or team of doctors treating the underlying cause of encephalopathy can offer the best information on the individual's prognosis (Häussinger, 2010).

### 3.7 Can encephalopathy be prevented?

Many cases of encephalopathy can be prevented. The key to prevention is to stop or limit the chance of developing any of the multitudes of causes of encephalopathy. If encephalopathy develops, the quicker the underlying cause is treated, the more likely it is to prevent the eruption of severe encephalopathy (Montgomery & Bajaj, 2011). Examples of prevention and avoidable situations are listed below: a) diabetic encephalopathy: daily check of glucose level and assurance of correct dosage of insulin; b) hepatic encephalopathy: avoidance of alcohol intoxication, drug overdose, and IV injections of illegal drugs; c) anoxic encephalopathy: prevention of food choking, avoidance of risky behavior that could lead to head and neck trauma, and exposure to carbon monoxide; d) hypertensive encephalopathy: monitoring of blood pressure; use of antihypertensive medication as directed and not quitting medications or changing medication without consulting the doctor; e) infectious encephalopathy: eluding physical contact with individuals known to be infected with organisms that may cause encephalopathy such as *N. meningitidis* or *Shigella*; f) uremic encephalopathy: do not skip or avoid scheduled dialysis, taking all medications as directed and having frequent assessment of mental status. Methods for prevention of encephalopathy are almost as numerous as the underlying causes. However, some cases of encephalopathy may not be preventable especially those originating from congenital cause or traumatic accident.

Therefore and as mentioned earlier, the key to therapeutic follow-up of any encephalopathy is to understand the underlying mechanism of the pathology and thus propose the best

treatment scheme. In this sense, microdialysis may contribute to understanding these basic mechanisms of encephalopathy, as well as to the possible application of pharmacological treatments that could restore or improve brain function of the patients, and in this way improve the quality of life of those suffering from this problem.

## 4. Microdialysis: Contributions in the study of encephalopathy

### 4.1 Encephalopathy induction mechanisms

#### 4.1.1 Hepatic encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric disorder that often occurs as a consequence of acute or chronic liver failure where hyperammonemia plays a major role in the pathogenesis of the disease. Hyperammonemia leads to altered cerebral function and neurological alterations in patients with hepatic encephalopathy. Studies with pigs showed that there is an association between extracellular brain ammonia and intracranial pressure (ICP), given that the concentration of ammonia in the brain, when it gets to about 1,200 microM of arterial accumulated ammonia, increases ICP. This result suggests that ICP could serve as a sensitive marker for HE development (Zwirner *et al.*, 2010). Also, Szerb and Redondo (1993) suggest that ammonia alters the function of astrocytes, facilitating their entry into the brain. This physiological event contributes to the development of HE. This was demonstrated with local administration of fluoroacetate in rats' hippocampal dentate gyrus using microdialysis (Szerb & Redondo, 1993).

Other studies have permitted the elucidation of the role of glutamatergic system and its receptors in HE. In 1996, Bergqvist *et al* tried to explain the participation of quinolinic acid (QUIN; a potent N-methyl-D-aspartate, NMDA-receptor agonist) and L-tryptophan (L-TRP) in HE. However, they did not find evidence suggesting their participation on observing that QUIN level and QUIN/L-TRP ratio were significantly low in rats subjected to a portacaval shunt (PCS), and that elevated L-TRP availability increased QUIN levels in a similar degree in both sham and PCS rats (Bergqvist *et al.*, 1996). Whereas in rats with ischemic liver failure induced by portacaval anastomosis followed by a 24-hr hepatic artery ligation, a significant threefold increase of extracellular glycine (a positive allosteric modulator of NMDA receptor) measured by *in vivo* cerebral microdialysis was found suggesting the participation of NMDA-mediated excitatory neurotransmission in this pathological condition (Zwingmann *et al.*, 2002). In other studies carried out to determine the role of NMDA receptors, it was shown that blocking these receptors by continuous administration of MK-801 or memantine (NMDA receptor antagonist) induces protection against acute liver failure (ALF) caused by galactosamine in experimental animals. This blockage increased the survival time by two folds. Also, when liver injury is not 100% lethal (1.5 g/kg galactosamine), blocking NMDA receptors increases the survival rate from 23 to 62% (Cauli *et al.*, 2008). On the other hand, there is experimental evidence that NMDA activation can be modulated by glutamate-nitric oxide-cyclic guanosine monophosphate (cGMP) pathway in ammonia intoxication in the cerebellum of the rats. However, it was found that this activation is not caused by increased extracellular glutamate (Hermenegildo *et al.*, 2000), but due to the presence of ammonium in high concentration in the brain. This was shown by Suzuki *et al* in 1992, who studied using microdialysis the brain extracellular fluid (ECF) amino acid metabolism and regional level elevation of ammonia in rats with hyperammonemia, experimentally induced through

administration of local intracerebral ammonia infusion. They found that total brain ECF amino acid level was increased by the elevation of blood ammonia and that in rats with hyperammonemia, there was an increased permeability of the blood-brain barrier. Also, they observed that only glutamate levels showed a marked elevation suggesting that high ammonia levels may increase the excitability of the brain and this situation may serve as a key to the onset of HE (Suzuki *et al.*, 1992).

In addition, other experimental data showed a significant increase in extracellular hippocampal glutamate concentration in rats thioacetamide-induced liver failure (McArdle *et al.*, 1996). Moreover, other studies suggest that the beneficial effect of hypothermia (35°C) in rats with hepatic devascularization that induces ALF is mediated via mechanism involving reduced blood-brain transfer of ammonia and/or reduction of extracellular brain glutamate concentrations (Rose *et al.*, 2000). It was also found that extracellular glutamate increased in substantia nigra pars reticulata (SNr) of rats with chronic liver failure due to portacaval shunt (PCS), and that this provoked activation of mGluR1 in SNr which together were responsible for reduced motor activity in these rats (Cauli *et al.*, 2006).

On the other hand, it was demonstrated that the involvement of glutamate-nitric oxide-cyclic guanosine monophosphate (cGMP) pathway in brain contributes to cognitive impairment in HE. Rodrigo *et al.* (2007) analyzed glutamate-nitric oxide-cGMP pathway function and nitric oxide synthase (NOS) activation by NMDA in an *in vivo* microdialysis in cerebral cortex of portacaval shunt (PCS) as well as in control and hyperammonemia rats without liver failure. They demonstrated that basal NOS activity, nitrites and cGMP are increased in cortex of rats with hyperammonemia or liver failure. These results are associated to increased inducible NOS expression. In both animal models and in neurons exposed to ammonia, impairment in NOS activation by NMDA was found while in chronic liver failure, basal NOS activity, nitric oxide and cGMP increased whereas activation of NOS induced by NMDA receptors activation decreased. Their results are evidence that hyperammonemia is responsible for both effects and these alterations could contribute to neurological alterations in HE (Rodrigo *et al.*, 2007). Additionally, there is an evidence indicating that hyperammonemia increases tonic activation of NMDA receptors leading to reduced activity of nNOS and of glutamate-NO-cGMP pathway. This was demonstrated by ElMlili *et al.* (2010), where the blockade of NMDA receptors with MK-801 increases cGMP and NO metabolites in cerebellum in *in vivo* and in slices from hyperammonemic rats. This was due to the reduction of the phosphorylation and activity of calcium-calmodulin-independent protein kinase II (CaMKII), leading to normalization of nNOS phosphorylation and activity. Also in these experiments, MK-801 increases nNOS in synaptic membranes and reduces it in cytosol (ElMlili *et al.*, 2010).

There is an evidence suggesting that not only glutamatergic neurotransmission is altered. It has been proposed that alterations of excitatory and inhibitory amino acids play a role in the pathogenesis of hepatic encephalopathy in ALF. This was determined *in vivo* cerebral microdialysis using extracellular concentrations of amino acid samples in the frontal cortex of non-anaesthetized rats at various times during the progression of encephalopathy resulting from ALF (induced by portacaval anastomosis). The amino acids from dialysate were measured by high-performance liquid chromatography (HPLC) with fluorescence detection and the results showed that the deterioration of neurological status was accompanied by two to four-fold increases in extracellular glutamate, glutamine, and



glycine while concentrations of gamma - aminobutyric acid (GABA) and taurine levels remained unchanged. These results suggest that amino acid could contribute to the pathogenesis of HE induced by ALF (Michalak *et al.*, 1996). However, these results are not convincing because they depend on the method of inducing ALF which can produce different changes in the level of amino acid. This is supported by the studies of Bosman *et al* (1992), who depicted that following microdialysis determinations in the cerebral cortex of rats with acute hepatic encephalopathy induced by complete liver ischemia, extracellular concentrations of the neuroactive amino acids glutamate, taurine, and glycine increased, whereas extracellular concentrations of aspartate and GABA were unaltered and glutamine decreased (Bosman *et al.*, 1992). Also, in cerebral cortical microdialysates of rats with subclinical hepatic encephalopathy (SHE) induced by two intraperitoneal injections of thioacetamide, it was found that dialysate concentrations of the neuroactive amino acids taurine (Tau), glutamate (Glu) and aspartate (Asp) were 30% to 50% higher in SHE rats than in control rats (Albrecht *et al.*, 2000).

Other reports demonstrated that the precursors of monoamines, as well as monoamines together with their metabolites, altered neuronal excitability and contribute to the characteristics of HE. Deshpande *et al* (2007) showed that in frontal cortex of rats with HE induced by ALF resulting from portacaval anastomosis followed by hepatic artery ligation, the extracellular brain concentrations of aromatic amino acids (AAAs) and of valine and leucine (precursors of monoamine neurotransmitters) elevated by 2 to 4 folds following hepatic devascularization, and these increases were significantly correlated to arterial ammonia concentration (Deshpande *et al.*, 2007; Michalak & Butterworth, 1997). So, those alterations in monoaminergic system are present in HE. Likewise, the monoaminergic system and the dopaminergic system are affected in HE. Yano *et al.*, (2005) demonstrated that the extracellular concentration of 3,4-dihydroxyphenylacetic acid, a metabolite of dopamine, decreased by 39% of that in sham-operated animals, although the dopamine level did not change. However, when treated with flumazenil (benzodiazepine antagonist), there was complete abolition of the decrease in the metabolite. Although, in this study the glutamate level in the injured animals decreased to 42% of that in sham-operated animals, there was no increase in the glutamate levels in animals treated with flumazenil. Also in this study, it was shown that spontaneous motor activity decreased 24 hours after surgery in animals subjected to liver ischemia and that flumazenil treatment improved spontaneous the motor activity 5 minutes after administration, but this effect was not observed after 30 minutes. For this reason, these authors proposed that the restoration of the central dopaminergic function could be a relevant factor in the improvement of HE (Yano *et al.*, 2005).

Other researchers have determined that in hyperammonemic rats there are neurological and cerebral function alterations, as well as alterations on the modulation of motor and neurochemical functions. The locomotion induced by injection of mGluR agonist dihydroxyphenylglycine (DHPG) in the nucleus accumbens increased. Also in control rats, DHPG increased extracellular dopamine (400%), but glutamate remained unchanged. Whereas in hyperammonemic rats, DHPG increased extracellular glutamate (600%), and when mGluR1 receptor was blocked with 7-hydroxyiminocyclopropan[b]chromen-1a-carboxylic acid ethylester (CPCCOEt), this treatment prevented DHPG effects, suggesting that this receptor mediates locomotor and neurochemical effects and showed that modulation of locomotor and neurochemical functions by mGluRs in nucleus accumbens is strongly altered in hyperammonemia (Canales *et al.*, 2003).

In addition, it was demonstrated that in rats with acute HE induced by repeated administration of thioacetamide, the impairment of modulation of striatal DA discharge and metabolism by the action of glutamate on NMDA receptors, contribute to motor disturbances in this disease (Borkowska *et al.*, 1999). Cauli *et al.* (2007) demonstrated that the function of the circuits that modulate motor function in rats with liver failure due to portacaval shunt (PCS) is dependent on the kind of neurotransmission. They found this result by analyzing the function of the circuits that modulate motor function in rats with liver failure due to portacaval shunt (PCS) using *in vivo* brain microdialysis. They inserted cannulae in the NAcc (where injected (S)-3,5-dihydroxyphenylglycine, DHPG) and microdialysis probes in NAcc, ventral pallidum (VP), substantia nigra pars reticulata (SNr), medio-dorsal thalamus (MDT), ventro-medial thalamus (VMT) or prefrontal cortex (PFCx) and analyzed the concentration of extracellular neurotransmitters in these areas. Their results indicate that in control rats, DHPG induces locomotion by activating the normal neuronal circuit: NAcc --> VP --> MDT --> PFCx and in PCS rats this circuit is not activated but DHPG injection in PCS rats activates an alternative circuit: NAcc --> SNr --> VMT --> PFCx that is not activated in control rats. These experiments suggest that dopamine increase induced by DHPG would activate the normal neuronal circuit, while an increase in glutamate would activate the alternative circuit (Cauli *et al.*, 2007).

On the other side, serotonergic system is also affected in HE. This was demonstrated by Bergqvist *et al.* (1996) who showed that frontal neocortical extracellular levels of 5-hydroxytryptamine (5-HT) is unaltered while its major metabolite, 5-hydroxyindole-3-acetic acid (5-HIAA), is increased in portacaval shunted rats in an experimental model of chronic hepatic encephalopathy (HE), prior to and after an acute coma-induction by the administration of ammonium acetate (5.2 mmol/kg, *i.p.*). These results suggest that an increase in brain ammonia may augment neuronal 5-HT release in HE, which in turn could be a causative of severe stages of HE (Bergqvist *et al.*, 1996).

In addition, in frontal cortex of rats with thioacetamide (TAA)-induced HE, it was found that 5-HIAA and high K<sup>+</sup>-evoked 5-HT release increased in HE rats. These data support the idea that serotonergic neurotransmission is altered in this brain area of rats with this pathology (Kaneko *et al.*, 1998).

Like other systems affected in HE, there is an experimental evidence suggesting that noradrenergic system is affected and describes that central noradrenergic mechanisms may contribute to the central nervous system manifestations of HE. Michalak *et al.* (1998) showed that there is an increase of extracellular brain concentrations of noradrenalin (NA), from the extracellular compartment of frontal cortex and thalamus in rats with acute liver failure (Michalak *et al.*, 1998), and this is associated to the loss of NA transporter sites resulting from depletion of central NA stores due to a reserpine-like effect of ammonia which is known to accumulate in brain in ischemic liver failure (Michalak *et al.*, 2010). These experimental data suggested that noradrenergic neurotransmission may play a role in this pathology.

On the other hand, there is an evidence that extracellular glutathione (GSH) is involved in the ammonia toxicity present in rats with HE. This was demonstrated by Hielgier *et al.* (2010) where the administration of ammonium chloride (ammonia) via a microdialysis probe to the rat prefrontal cortex increased GSH. This increase was abrogated by the inhibitor of

astrocytic energy metabolism of fluoroacetate and inhibitor of glutathione synthesis of buthionine sulfoximine. Their results suggest that in rats with hyperammonemia HA or HE ammonia specifically promote GSH synthesis may improve the availability of precursors for GSH synthesis in neurons and their resistance to ammonia toxicity present in HE (Hilgier *et al.*, 2010).

#### 4.1.2 Fulminant hepatic encephalopathy

Fulminant hepatic encephalopathy is one of the encephalopathies with high mortality. To find chemical markers that provide information leading to application of the best therapeutic treatment in these patients is a priority. The microdialysis, being a highly sensitive technique in monitoring cerebral energy metabolism and in early detection of cerebral hypoxia has been used to find these chemical markers. Beuer *et al* (2004) were the first in reporting a case of monitoring neurochemical markers using intracerebral microdialysis during cardiac resuscitation. They measured the chemical markers of energy metabolism of glucose, lactate, pyruvate, and the marker of cell membrane damage (glycerol) and found that except subcutaneous glucose, all markers showed a sudden and significant increase during resuscitation and a prolonged period afterwards with all values returning to normal after some hours (Bauer *et al.*, 2004). In another study to determine the role of cerebral microdialysis as an adjunct to the management of a 49-year old woman with hepatic encephalopathy secondary to a paracetamol overdose, it was found that the application of the microdialysis technique for the detection of cerebral glucose concentration in the presence of a normal plasma glucose was useful for the continuous on line monitoring of substrate delivery and metabolism, and this may have a relevant role in the therapeutic management of patients with fulminant hepatic failure (Hutchinson *et al.*, 2006).

#### 4.1.3 Posthypoxic encephalopathy

Actually, there is only one study that focused on determining the neurochemical alterations in a seemingly posthypoxic encephalopathy. Thoresen *et al* (1998) studied changes in lactate and pyruvate in gray and white matter in the brain of a newborn pig after a hypoxic insult known to produce seizures and permanent brain damage. They induced hypoxia for forty-five minutes by reducing the fraction of inspired O<sub>2</sub> to the maximum concentration and found that there was no association between onset of electroconvulsive activity and an increase in lactate or lactate/pyruvate (L/P) ratio which are the biochemical parameters altered in posthypoxic encephalopathy (Thoresen *et al.*, 1998).

#### 4.1.4 Hypoxic-ischemic encephalopathy

Pearing *et al* (1996) studying the effect of hypoxia in-vivo, separately analyzed the hypoxic component of hypoxic-ischemic encephalopathy. They used rats that were prepared such that their arterial oxygen pressure (paO<sub>2</sub>) was maintained at 20 mmHg. While maintaining systemic arterial pressures, the brain oxygen concentration and extracellular amino acid concentrations were monitored during 20 minutes. They did not find changes in the extracellular glutamate extracellular levels, and with additional experiments no morphologic injury was detected. Thus, they conclude that hypoxia without ischemia is well tolerated by the brain (Pearigen *et al.*, 1996).

#### 4.1.5 Encephalopathy associated with septic shock

Encephalopathy associated with septic shock as well as neurological disease could be induced by the central nervous formation of reactive oxygen species (ROS) associated with inflammation process. Clement *et al* (2010) analyzed the effect of peripherally applied lipopolysaccharide (LPS, 100 mug/kg i.p.) that is used as a model for major depression and results in enhanced inflammatory processes, on the central nervous formation of ROS and interleukin-6 (IL-6) in wild-type mice and in mice lacking NADPH oxidase Nox2 subunit gp91phox using microdialysis paradigm. They found that in the wild-type mice, LPS increased ROS formation in the striatum of wild-type mice and resulted in enhanced IL-6 production. In the mice lacking NADPH oxidase Nox2 subunit gp91phox, LPS did not enhance ROS formation, whereas IL-6 increased. They conclude that gp91phox-containing NADPH oxidase complex was involved in the central nervous ROS formation after peripheral LPS stimulation and these results suggest that ROS determination could be a pharmacological target in patients with this pathological condition (Clement *et al.*, 2010).

#### 4.1.6 Thiamine deficiency encephalopathy (Wernicke)

The Wernicke encephalopathy is characterized by thiamine deficiency. This pathology is a neurological disease detected in alcoholics and in patients with compromised nutrition. Todd *et al* (2001) established the role of glutamate excitotoxicity using in vivo microdialysis in the neuronal cell death due to thiamine deficiency, with the considerations of different factors (blood-brain barrier, tissue reactions to probe implantation) that may affect the probe recoveries (Todd & Butterworth, 2001). In addition, Todd and Butterworth (1998) evaluated the role of NMDA receptor-mediated glutamate excitotoxicity in the pathogenesis of neuronal loss induced by thiamine deficiency. They also determined extracellular glutamate levels using in vivo cerebral microdialysis in the ventral posterior medial thalamic nucleus. Their result suggests that NMDA receptor-mediated excitotoxicity is not responsible for early neuronal loss in this model of thiamine deficiency encephalopathy (Todd & Butterworth, 1998).

Other studies were directed to the study of the role of histamine in neuronal degeneration in a rat model of Wernicke's encephalopathy induced by pyriithiamine-induced thiamine deficiency (PTD). They established that the histamine enhancement of glutamate receptor activation suggests that the histamine release could be a participant in glutamate-N-methyl-D-aspartate (NMDA)-mediated excitotoxic neuronal death in this pathology (Langlais *et al.*, 1994). And, that the release of histamine in rat from nerve terminals and histamine and other vasoactive substances from granulocytes could be responsible for thiamine deficiency-induced vascular breakdown and perivascular edema in thalamus (McRee *et al.*, 2000).

#### 4.1.7 Viral encephalopathy

Espey *et al* (1998) determined in mice infected with LP-BM5 leukemia retrovirus mixture that develop a progressive immunodeficiency with associated behavioral, histological, and neurochemical alterations consistent with glutamatergic hyperactivation. They clarify the contribution of excitatory amino acids to the neurodegeneration observed in these mice by measuring extracellular glutamate levels in the striated brain area of these animals, and found that infection with an immunodeficiency-inducing retrovirus increases extracellular



free glutamate levels in this brain region. Based on this, they suggest that these changes contribute to neurodegenerative and cognitive deficits observed in this experimental model of viral encephalopathy (Espey *et al.*, 1998).

#### **4.1.8 Portal-systemic encephalopathy**

Portal-systemic encephalopathy (PSE) is characterized by psychiatric symptoms progressing through stupor and coma. Actually, there is experimental evidence suggesting that alterations in levels of brain amino acids may play a role in the pathogenesis of PSE. Rao *et al* (1995) studying this changes, did found changes in extracellular fluid concentrations of glutamate, aspartate, GABA, tryptophan, leucine, and serine in cerebral frontal cortex of portacaval-shunted rats that were administered ammonium acetate (3.85 mmol/kg, i.p.) to induce PSE. (Rao *et al.* 1995).

In addition, PSE is associated with an increased brain tissue of serotonin (5-HT). The involvement of serotonergic neurotransmission was demonstrated by Bergqvist *et al* (1996, 1997) who found that potassium chloride (KCl) challenged induced increase of 5-HT release in neocortical region of the rats with a portacaval shunt (PCS) (Bergqvist *et al.*, 1996, 1997).

### **4.2 Microdialysis applied in the study of encephalopathy therapeutic treatments**

#### **4.2.1 Hepatic encephalopathy**

##### **4.2.1.1 L-ornithine and L-ornithine-L-aspartate study**

Vogels *et al* (1997) established that the L-ornithine (ORN) and L-ornithine-L-aspartate (OA) therapeutic treatment had a beneficial effects on the symptomatologies of rats with hyperammonemia-induced encephalopathy by portacaval shunted for the fact that ORN and OA treatments decrease ammonia concentrations in blood by 34% and 39%, and in brain by 42% and 22%. Also they found that these substances increased urea production by 39% and 86%, with a significant smaller increase in brain glutamine and lactate concentrations than in controls. However, the effect of ornithine should be taken with care due to the fact that this substance induces high brain extracellular levels of glutamate and aspartate (excitatory amino acids), suggesting a possible overstimulation of NMDA receptors (Vogels *et al.*, 1997).

##### **4.2.1.2 Venlafaxine studies**

Patients with chronic hepatic encephalopathy (HE) may present affective symptoms and antidepressant drug treatment due to HE displays monoaminergic perturbations together with affective symptoms. Venlafaxine (VEN) is an antidepressant, and serotonin-norepinephrine reuptake inhibitor that is used in the treatment of patients with HE. The liver impairment present in HE patients may induce pharmacokinetic alterations of antidepressant drug, which in turn can modify monoaminergic function. Because of this, Wikell *et al* studied this possible alterations, and determined that in rats with chronic portacaval shunted (PCS; experimental hepatic encephalopathy), VEN (10 mg/kg) administered in a unique doses (subcutaneous) and daily during 14 days (continuous delivery by osmotic minipumps) exhibits both pharmacokinetic and pharmacodynamic alterations in these rats (Wikell *et al.*, 1998, 2002).

When VEN was administered at 5 mg/kg as a single subcutaneous challenge to portacaval shunted rats, it resulted in elevated levels of VEN in serum, brain parenchyma, and brain dialysate in about 300 minutes after the injection. Therefore, this result suggests that when the dose of VEN administered to experimental HE was reduced 50%, important pharmacokinetic alterations are presented in these animals (Wikell *et al.*, 2001), in the same way that the studies done with dose of 10 mg/kg (Wikell *et al.*, 1998, 2002).

#### 4.2.1.3 Citalopram studies

Citalopram (CIT) is an antidepressant drug of the selective serotonin reuptake inhibitor used in patients with HE that display neuropsychiatric symptoms like affective disturbances. The simultaneous pharmacokinetic and pharmacodynamic outcome of the commonly used serotonin-selective thymoleptic drugs in liver-impaired subjects with HE is not totally understood today.

Bergqvist *et al* (1997) studied the effects of neocortical administration of CIT (1.0 microM), and CIT (5 mg/kg subcutaneously) on brain 5-hydroxytryptamine release in portacaval shunted rats with an experimental chronic hepatic encephalopathy. They found that neocortical administration of CIT increased the brain 5-HT output in the same way as in portacaval shunted sham-operated rats. These data do not explain the increased 5-HT turnover and unchanged release in PCS rats by an accelerated brain 5-HT reuptake. For this reason, the administration of CIT (5 mg/kg subcutaneously) resulted in a pronounced decrease of brain 5-HT release in PCS rats than in sham-operated controls. This may be due to a higher susceptibility to indirect 5-HT<sub>1A</sub> autoreceptor activation in experimental portal-systemic encephalopathy. Their experiments with potassium chloride (60 mM) challenge in the presence of locally CIT (1 microM) induced an increase of 5-HT response in PCS rats than in sham-operated rats, confirmed an abnormal increase of 5-HT available for depolarization-induced release in PCS rats. These results suggested that central nervous system 5-HT-active drugs could perhaps pose a potential hazard in patients with liver failure with or without HE (Bergqvist *et al.*, 1997).

In addition, Apelqvist *et al* (2000) investigated the effects of chronic treatment with CIT (10 mg/Kg day) in the frontal neocortex of rats with and without portacaval shunts in 5-HT, 5-HIAA, noradrenaline (NA), and dopamine (DA) output. The rats with PCS increased by 2-3 folds the levels of CIT than rats undergoing a sham treatment with CIT in all compartments. This treatment induced in neocortical output differences between PCS rats and control rats within 5-HT and DA systems but not in NA system. Their data suggest pharmacokinetic and pharmacodynamic changes in an equal-dose chronic treatment with CIT in PCS rats, changes that were not observed in sham rats. Interestingly, these authors indicate that although there are pharmacokinetic and pharmacodynamic alterations with CIT-treatment in PCS rats, the beneficial behavioral response remains (Apelqvist *et al.*, 2000).

#### 4.2.1.4 Lubeluzole study

Lubeluzole is a neuroprotectant which is effective in the treatment of experimental stroke in rats, mainly by inhibition of glutamate-activated NO pathway and also by counteracting osmotic stress (mechanism associated to the release of the active amino acid taurine). Zielinska *et al* (2001) showed that lubeluzole administered intraperitoneally decreases by 25% the high (50 mM) K<sup>+</sup>-evoked accumulation of Taurine (Tau) in striatal microdialysates

of healthy rats and by 34% in rats with thioacetamide-induced hepatic failure, suggesting increased extracellular of Tau in ongoing hepatic encephalopathy. These data indicate that lubeluzole could be effective in ameliorating ionic or osmotic stress in rats with hepatic failure (Zielińska *et al.*, 2001).

#### 4.2.1.5 Sildenafil study

Patients with liver disease with overt or minimal hepatic encephalopathy have impaired intellectual capacity and the underlying molecular mechanism remains unknown. Interestingly, rats with portacaval anastomosis or with hyperammonemia without liver failure also show impaired learning ability and impaired function of the glutamate-nitric oxide-cyclic guanine monophosphate (glutamate-NO-cGMP) pathway in brain. Erceg *et al* (2005) hypothesized that pharmacological manipulation of this pathway (glutamate-NO-cGMP) could restore learning ability. They showed that in vivo brain microdialysis, chronic oral administration of sildenafil (an inhibitor of the phosphodiesterase that degrades cGMP), normalizes the function of the glutamate-NO-cGMP pathway and extracellular cGMP in the brain of rats with portacaval anastomosis or with hyperammonemia. They determined that impairment of learning ability in rats with chronic liver failure or with hyperammonemia are the result of impairment of glutamate-NO-cGMP pathway and that the chronic treatment with sildenafil normalizes the function of the pathway and restores learning ability in rats with portacaval shunts or with hyperammonemia (Erceg *et al.*, 2005).

#### 4.2.1.6 Ibuprofen study

Patients with hepatic encephalopathy show altered motor function, psychomotor slowing, and hypokinesia, which are reproduced in rats with portacaval shunts (PCS, an experimental model of HE). The neurochemical alterations induced by hypokinesia in PCS rats are attributed to the increase of extracellular glutamate in substantia nigra pars reticulata (SNr), but the mechanisms by which liver failure leads to increased extracellular glutamate in SNr remain unclear. However, it was seen that inflammation acts synergistically with hyperammonemia to induce neurological alterations in hepatic encephalopathy and by this way, the inflammation alterations can contribute to motor alterations in HE. For this reason Cauli *et al* (2009) assessed if the treatment with an anti-inflammatory, ibuprofen, is able to normalize extracellular glutamate in SNr and/or improve hypokinesia in PCS rats. They found that ibuprofen at 15 or 30 (but not at 5 mg/kg/day), completely eliminates hypokinesia and restore normal motor activity. This supports the supposition that inflammation is the principal contributor to the induction of hypokinesia in HE and this data suggests that therapeutic treatment of inflammation in the motor deficits in patients with this pathology could be beneficial (Cauli *et al.*, 2009).

### 4.2.2 Hypoxic-ischemic encephalopathy

#### 4.2.2.1 Dichloroacetate study

Dichloroacetic acid, often abbreviated as DCA, the salts of which has been studied as potential drugs due to their inhibition of pyruvate dehydrogenase kinase enzyme. The common use of DCA is in the treatment of cancer, and actually several studies using adult animal models suggest that DCA may have neuroprotective properties by virtue of its ability to increase rates of metabolism and, therefore, clearance of brain lactic acidosis,

which may accumulate during cerebral ischemia. Corbett *et al* (1998) hypothesized that postischemic DCA administration affects lactate and acid clearance in different extents in immature versus mature brain. Their results indicate that postischemic DCA administration helps to resolve cerebral acidosis to a greater degree in immature than in more mature brain, and this suggests that DCA could have cerebroprotective properties for neonatal hypoxic-ischemic encephalopathy (Corbett *et al.*, 1998).

#### 4.2.2.1 Indomethacin study

Indometacin or indomethacin is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins, molecules known to cause these symptoms. To try understanding the role of this drug in the possible protective effect on hypoxic ischemic encephalopathy, Ogasawara *et al* (1999) examined the effects of indomethacin on extracellular dopamine (DA) in the striatum of immature rats submitted to anoxia using *in vivo* microdialysis and HPLC to quantify DA. They found that during anoxia the DA level reached 1185+/-400% of the basal level and the peak levels of DA were only 307+/-63%, 153+/-35% in indomethacin groups. They conclude that the suppression that induces indomethacin is possibly one of the mechanisms that helps to avoid the dopamine alterations on hypoxic ischemic encephalopathy (Ogasawara *et al.*, 1999).

## 5. Conclusions

Microdialysis is a powerful tool widely used in neurosciences. The use in Neurology has been on the increase on the discovery of its importance in understanding the possible mechanisms underlying neuropathies, and its application in the study of new therapeutic substances.

Although, the use in *in-vivo* experimental studies and in animal models dates back to years, now there is an increase in the tendency to use this technique to study the neuropathology in humans, and this has helped to make the most appropriate decisions for the treatment of patients. It is noteworthy that studies in humans are very limited, since they involve legal and ethical permissions, but however, data from the few studies in human have shown favorable results that have contributed to the implementation of specific treatments.

On the other hand, microdialysis is a technique that allows the measurement of molecules which may be involved in pathophysiological changes of various diseases as encephalopathy, finding molecular targets for early diagnosis and timely treatment of patients with this disease that result in the greater likelihood of remission and minimizing the potential consequences that such conditions could leave, improving the prognosis of these patients.

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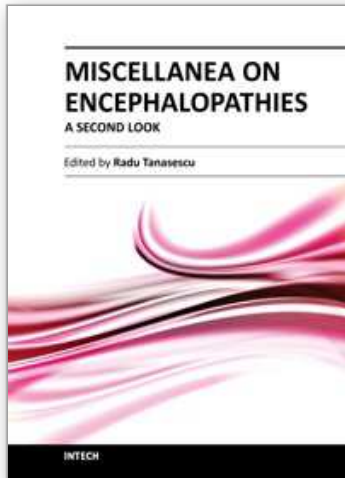


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Phone: +86-21-62489820  
Fax: +86-21-62489821



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