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Cerebral Microdialysis in Neurocritically ill Patients

An essay

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List of Contents

List of Abbreviations

ATP ..... Adenosine Tri-Phosphate

βAPP ..... Beta Amyloid Precursor Protein

BBB ..... Blood Brain Barrier

Ca2+ ..... Calcium

CBF ..... Cerebral Blood Flow

CE ..... Conformité Européene

CPP ..... Cerebral Perfusion Pressure

CSD ..... Cortical spreading depression

CSF ..... Cerebrospinal Fluid

CT ..... Computed Tomography

DAI ..... Diffuse axonal injury

ECF ..... Extracellular Fluid

FDA ..... Food and Drug Administration

F-P ..... Fluid-Percussion

GABA .... Gamma-Aminobutyric Acid

HRP ..... Horseradish peroxidase

ICBF ..... Intra Cerebral Blood Flow

ICP ..... Intra Cranial Pressure

ICU ..... Intensive Care Unit

IRB ..... Institutional review board

LCBF ..... Local cerebral blood flow

LTC method .. Level, Trend and Compare

MCA ..... Middle Cerebral Artery

MCAO ... Middle Cerebral Artery Occlusion

MD ..... Microdialysis

MRI ..... Magnetic Resonance Imaging

NAD+ ..... Nicotinamide Adenine Dinucleotide

NADH .... Nicotinamide Adenine Dinucleotide - Hydrogen (reduced)

PD ..... PharmacoDynamic

PET ..... Positron Emission Tomography

PID ..... Periinfarct depolarization

PK ..... PharmacoKinetic

PO2 ..... Partial pressure (tension) of oxygen

SAH ..... Sub Arachnoid Hemorrhage

TBI ..... Traumatic brain injury

TCD ..... Trans Cranial Doppler

List of Figures

LIST OF TABLES

INTRODUCTION

Historically, the only means to measure substances in the brain was after death by analyzing brain homogenate, but through the last two decades exciting progress has been achieved. Now it's available to directly measure brain extracellular chemicals by the microdialysis technique, and imaging techniques such as magnetic resonance spectroscopy. These techniques are used to measure chemical concentrations noninvasively. **(Johnston and Gupta, 2002)**

Cerebral microdialysis is a relatively new technique to measure the levels of brain extracellular chemicals; this review considers the process of brain cell death and ischemia, the importance of the commonly measured chemicals, technical aspects of microdialysis, and the uses of microdialysis to monitor patients with ischemic stroke, head injury, and subarachnoid hemorrhage **(Ungerstedt, 1991).**

AIM OF THE WORK

The aim of the work is to:

Study the procedure of cerebral microdialysis and its uses in neuro-intensive care.

Chapter 1:

PATHOPHYSIOLOGY OF BRAIN ISCHEMIA AND CELL DAMAGE

Current knowledge about the pathophysiology of cerebral ischemia and brain trauma elucidates that similar mechanisms lead to loss of cellular integrity and tissue demolition. Mechanisms of cell damage include excitotoxicity, oxidative stress, free radical production, apoptosis and inflammation. Genetic and gender factors show importance as mediators of pathological mechanisms present in both injury types. However, the fact that these injuries caused by different types of primary insults causes diverse cellular vulnerability modalities as well as a spectrum of injury processes. Blunt head trauma results in shear forces which cause primary membrane damage to neuronal cell bodies, white matter structures and vascular beds as well as secondary injury mechanisms. Severe cerebral ischemic insults cause metabolic stress, ionic disturbance, and a complex cascade of biochemical and molecular events finally causing neuronal death. Similarities in the pathogenesis of these cerebral injuries may indicate that therapeutic and prophylactic strategies following ischemia may also be useful after trauma. **(Bramlett and Dietrich, 2004)**

A) Cellular Vulnerability

In both brain ischemic and traumatic insults, patterns of neuronal vulnerability are well described. The neuron has classically been shown to be very sensitive to periods of cerebral ischemia. Decrease in blood flow reaching 25ml/100g/minute in rodents is considered severe enough to lead to definitive cell death. Vulnerability patterns are determined by the period of ischemia in addition to the severity of the ischemic insult. ***For example, a brief period of severe ischemia may lead to selective neuronal damage, with minor cellular changes observed in glia and blood vessels.*** However, with more ischemic periods, other cellular responses can be observed, producing ischemic infarction at the end. Cerebral blood vessels damage occurs with reperfusion injury, hemorrhagic transformation of infarcted tissue and severe brain swelling which can be produced by the activation of inflammatory processes. **(Dirnagl et al., 1999)**

In cases of cardiac arrest and transient forebrain ischemia, specific groups of neurons have been shown to be vulnerable. After cardiac arrest, the CA1 sector and dentate hilus of the hippocampus, dorsolateral striatum and Purkinje neurons in the cerebellum are most vulnerable. On the other side, focal ischemia leads to a

core of severe hypoperfusion surrounded by an area of viable tissue where blood flow is slightly decreased. However if the core is not reperfused, it ends in an ischemic infarct in which all cellular elements are destroyed. In severe focal ischemia, death of the neuron can occur in a few hours after the insult. However, neuronal death can take as long as 2–3 days to mature after periods of transient global or focal ischemia. This maturation phenomenon signifies the occurrence of a secondary injury which may indicate a prolonged ***therapeutic window*** for treatment strategies. (**Bramlett and Dietrich, 2004)**

The penumbra region surrounding the ischemic core has a preserved ionic state and may show scattered ischemic neurons in an intact neuropil **(Back, 1998)**. These cellular events may take hours to days for maturation, according to the nature of the ischemic insult and presence of perineuronal depolarizations. Following focal ischemia, multiple attacks of cortical spreading depression have been found and demonstrated in the penumbra as well as more distant regions of the brain. These propogating waves are due to intracellular calcium that causes depolarization of cells and results in metabolic stress and the induction of a variety of proteins and genes in areas far from the infarct **(Hossmann, 1996)**.

Patterns of both diffuse and focal neuronal injury can also be identified following human and experimental TBI. A common consequence of severe trauma is the formation of a hemorrhagic contusion caused by blunt head injury or a gliding insult. Both insults can directly injure blood vessels and neuronal membranes, including those of cell bodies and axonal processes. Severe injuries can cause damage of glial cells including astrocytes and oligodendrocytes. No doubt, glial swelling is one of the earliest cellular changes observed after contusion injury. **(Bramlett and Dietrich, 2004)**

Contusions are commonly associated with hemodynamic changes including local reductions in local cerebral blood flow (lCBF). In both clinical and experimental studies, the decrease in blood flow has been reported to correlate with the severity of injury. Thus, after mild to moderate TBI in experimental animals, decreases in flow are usually 70–80% of normal. However, with more severe injury, CBF approaches ischemic levels. It was reported in some clinical studies that ischemic levels of flow are only noticed in irreversibly damaged tissue **(Diringer et al., 2002).** In contrast, other studies in patients with head trauma have demonstrated histopathological changes consistent with hypoxic/ischemic insults and severe decrease in flow early after TBI **(Von Oettingen et al., 2002)**. Following

TBI, tissue PO2 is decreased in the traumatized tissue and, therefore, slight decrease in blood flow may have severe consequences on cellular survival. Experimental studies have reported reduction in ATP content in traumatized cortical areas and elevation in lactate levels following severe TBI. **(Lee et al., 1999)**

Focal areas of reduced CBF after brain trauma can be surrounded by regions with milder reductions in flow. This surrounding area may thus correspond to the penumbral region surrounding an ischemic core **(Back, 1998)**. This border zone area has scattered damaged neurons within an intact neuropil. Significantly, this area is sensitive to therapeutic measures as well as at risk for secondary insults. **(Bramlett and Dietrich, 2004)**

Although much is known about structural changes which occur early following cerebral ischemia or trauma, less is known about the progressive nature of these acute insults to the brain. Clinically, MRI is used to observe progression of damage in stroke and TBI patients. **(Baird et al., 1997)**

Experimentally, progressive atrophy of gray and white matter structures has been reported in models of TBI. In one study, severe atrophy of multiple white matter tracts was observed 1 year after TBI. Better

strategies for neuroprotection and reparative processes could be achieved through greater understanding of the pathophysiological processes in this underlying progressive injury cascade. **(Bramlett and Dietrich, 2004)**

B) White Matter Vulnerability

In addition to damage to gray matter structures, white matter vulnerability is observed in both ischemic and traumatic conditions **(Dewar et al., 2003)**. Because the normal function of the brain depends on the communication between brain regions, the illustration of mechanisms contributing to acute and/or progressive white matter injury is critical to the understanding of brain injury. **(Goldberg and Ransom, 2003)**

In this concern, the lack of successful human stroke trials explained as neuroprotective strategies have primarily targeted gray but not white matter structures. After focal cerebral ischemia, we can observe the damage to white matter tracts using a variety of chemical markers. **(Dewar et al., 1999)**

Abnormal beta amyloid precursor protein (ßAPP) immunoreactivity, an indicator of abnormal axonal transport has been reported in white matter structures in