Review Article

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The pathophysiology of post traumatic epilepsy

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Abstract: Posttraumatic epileptogenesis provides an opportunity for the clinician to study the phenomenon of seizurogenesis along with the process of apoptosis which is triggered by traumatic brain injury (TBI), there is a simultaneous effort at neuro regeneration, neo synaptogenesis and plasticity.

The seat of maximal neuronal changes after TBI is the hypothalamus. This loss of hilar cell inhibition of the hypothalamus on the CA_3 region of the dentate gyrus results in mossy fibre sprouting and an attempt at neo synaptogenesis. While neo synaptogenesis is associated with long term potentiation (memory), it can also result in seizurogenesis. Pharmacologic inhibition of epileptogenesis remains in the realm of experimental therapeutics, but is likely to replace conventional antiepileptic drugs in the preventive management of post traumatic seizure disorder.

Keywords: traumatic brain injury, hypothalamic neo synaptogenesis.

INTRODUCTION

Posttraumatic epilepsy is an enigma shrouded in mystery. Understanding the aetio pathogenesis of this entity offer the researcher the opportunity to study the phenomenon of epileptogenesis[1].

To understand the aetiopathogenesis of post traumatic epilepsy, it is important to appreciate the cascades after trauma. The process of ongoing neural damage after trauma occurs simultaneously with an attempt at neural repair[2]. Animal experiments using rats of traumatic brain injury (TBI) have used fluid percussion injury as the injuring mechanism. The secondary processes of neuronal apoptosis and regeneration are most marked in the hippocampal region[3]. In the coming paragraphs we discuss, the ongoing molecular and cellular changes culminating in a spectrum of neurochemical and synaptic aberrations or in apoptosis[4]. We attempt to elucidate as to how aberrations in these process result in epilepsy.

The cascade of Secondary Neuronal Injury after TBI

Stretch injury is the commonest mechanism of neuronal injury. Mechanically this result in a sliding of the lipid bilayer of the cell membrane from the protein receptors and channels resulting in a phenomenon described as mechano - poration. There is a release of excitotoxic amino acids, causing further disturbance to the ionic pump mechanisms, resulting in the escape of potassium to the extracellular space and an ingress of calcium into the cell[5]. Simultaneously, there is a breach in the blood brain barrier and the release of Intracellular adhesion molecules resulting in the ingress of leukocytes[6]. This leukocytic ingress triggers off inflammatory cascades further poisoning the ionic pump[7].

Intracellular calcium activates phospholipases causing free fatty acid release[8] and the release of oxygen frees radicals[9]. This is mediated by the prostaglandin pathway. Free fatty acids damage the blood brain barrier[10]. Reactive oxygen radicals induce nuclear (DNA) damage[11]. Intracellular Calcium also triggers off cyto skeletal disruption by activating calpains which cause proteolysis of tubulin and spectrin (cyto skeletal proteins)[12]. Increased intracellular calcium also poisons the mitochondria resulting in a neuronal metabolic failure[13].

There is possibly an Aetiological correlation between head injury and Alzheimer's disease[14]. The significance of the apolipoprotein E-gene as a risk factor in neurological injury cascades gives a clue as to why different patients progress differently after neuronal insults. The culmination of the neuronal damage is in apoptosis and this is mediated through caspases. Caspases 8 and 9 are described as initiator caspases and caspase 3 is called the executioner caspase[15].

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The ingredients of neuronal recovery

The concept that neuronal loss after trauma is permanent has been challenged in the context of current knowledge. Neuronal recovery does occur, by a combination of neuronal plasticity, axonal regrowth and from replacement by multiplying neuronal progenitor cells. These neuronal stem cells are mobilised predominantly from the dentate gyrus of the hippocampus (03) and migrate to the areas of injury. Neuronal plasticity involves the transfer of function of damaged neurons to intact neurons[16] and involves both the re organisation of old synaptic connections and the establishment of new ones[17].

The role of glia in the restorative process has been the topic of much debate. Far from being an inert scar, proliferating glial cells consist in the restoration of the ionic balance. They also secrete various neuro trophic factors [18].

Post Traumatic Synaptogenesis: Is epileptogenesis synonymous with aberrant repair

There is a selective vulnerability of hippocampal neurons to neurotrauma[1]. The CA 3 neurons of the dentate gyrus[3] of the hypothalamus have regenerative potential. Post traumatic epileptogenesis possibly has its origins in this region. The factors contributing to epileptogenesis include disturbances in the ionic milieu and neuronal synaptic changes.

Disorganization of the ionic milieu

Membrane depolarization during neuronal electrical activity results in an extracellular accumulation of potassium. This potassium has to be removed from the extracellular region by the ionic pump as well as by glial cell uptake and spatial dispersal. Both these mechanisms fail in a post trauma setting. The well defined entity of post traumatic ATP depletion results in a failure of the ionic pump[19]. Contrary to popular perception astrocytes are more sensitive to stretch injury than neurons[20]. The failure of the astrocyte energy milieu following TBI causes a failure of astroglial uptake and redistribution of potassium[21]. This results in altered resting membrane potentials and neuronal excitability, with a loss of inhibitory postsynaptic potentials due to a GABA induced inhibition of inhibitory interneurons.

Bursters and Spikes: the influence of Potassium

Based on their electrical activity, neurons can be grouped into spikers & bursters. Spikers are neurons that generate a single spike in response to a brief current. Bursters, on the other hand, generate a cluster o spikes riding the shoulder of slow membrane depolarization. Neurons with burster characteristics are predominantly found in the CA3 sub region of the hypothalamus. An increase in extracellular K^+ has been shown to shift neurons from a spiker to a burster state[1].

The Excito toxicity of Glutamate

Extracellular glutamate levels are elevated after traumatic brain injury. Glutamate toxicity acts on the NMDA receptors, causing a magnesium resistant blockade and calcium ingress into the cell[22]. Calcium ingress results in long term Potentiation without depression and a hyper excitable state[23].

Glutamate Homeostasis after TBI

Mechanically injured cells release glutamate[24]. Glial glutamate transporter protein [GLT] is involved in the regulation of extracellular glutamate levels. Levels of GLT are shown to be decreased after TBI especially in the neocortical and hippocampal regions[25].

Neuronal Sprouting

Following trauma induced neuronal loss, restorative changes are triggered by Neurotrophic factors in the hippocampus. These processes include axonal sprouting, neo synaptic genesis and dentate gyrus (CA3) region proliferation of progenitor cells[26]. Mossy fibre axonal sprouting after & neuronal loss is associated with attempts at functional reorganization. Disorganization in this neo synaptogenesis process results in epileptogenesis[27]. Mossy fibre sprouting can be induced in the rat model by provoking status epilepticus by electrical stimulation of the amygdala[28]. Mossy fibre sprouting can also occur without seizures during the process of long term potentiation i.e. memory and learning[29] Hippocampal neosynptogenesis results in both neuronal functional recovery and epileptogenesis. To block one while facilitating the other is the challenge[30].

The Phenomenon of Dentate Gyrus Disinhibition

The hilar neuron cells of the hippocampus are

preferentially lost in the fluid percussion TBI model[31]. Normally hilar neurons exert an inhibitory effect on the dentate gyrus. The loss of hilar disinhibition is a potential mechanism of seizure induction[32].

The Phenomenon of Kindling - Is it relevant as an epileptogenic mechanism

Repeated stimulation results in a progressive lowering of the seizure threshold. This phenomenon is called kindling. Kindling is propounded as the mechanism by which secondary seizure foci are established in long standing seizure disorders. However, the classic anti-epileptic drugs are not anti epileptogenic i.e. they control post traumatic seizures, but do not prevent the establishment of seizure foci. Tetradoxin, a sodium channel blocker, has been used in the rat model successfully, to prevent epileptogenesis[33].

CONCLUSION

An understanding of the secondary changes occuring after a traumatic brain injury, is the key to understanding the phenomenon of epileptogenesis[34]. The cascades occuring after traumatic brain injury have been evaluated with micro-dialysis[35]. The ongoing apoptotic process of diffuse axonal injury have been evaluated[36]. Animal models have provided evidence for both hippocampal cell loss after trauma and the sometimes disorganised synaptogenesis that culminates in epileptogenesis[1,32]. However, drugs which can prevent epileptogenesis have yet to be tried in humans[30,33]. Until this is achieved, posttraumatic epilepsy will continue to be managed symptomatically with standard antiepileptic drugs[37].

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