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Chapter VI

Neurobiology of the CNS injury and repair: New roles of amino acids, growth factors and neuropeptides – Introduction

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Injury to the central nervous system (CNS) induces a series of complex neurochemical events leading to widespread cellular and molecular alterations causing cell injury or cell death. These complex events are triggered by the initial primary injury that are progressive in nature. Several neurochemical agents are released simultaneously following the primary insult that contributes to the secondary injury cascade, a concept first proposed by Allen (1911). One of the most important events following trauma to the CNS is a breakdown of the microvascular permeability caused by the release of these neurochemical agents (Stålberg et al., 1998). An increased permeability of the blood-brain barrier (BBB) allows extravasation of the serum proteins into the brain extracellular fluid compartment leading to the vasogenic edema formation. Progression and persistence of edema in a closed cranial compartment will cause severe brain compression. This will result in local ischemia, perturbation of cellular energy metabolism and cell death (Sharma and Westman, 1998). Similarly, edema formation in the spinal cord results in myelin vesiculation and axonal damage causing sensory and motor dysfunction (Stålberg et al., 1998).

Thus, efforts should be made to expand our knowledge regarding the cellular and molecular mechanisms of the BBB disturbances in CNS injuries. The building blocks of the BBB are endothelial cells that are connected with tight junctions. The spinal cord is also equipped with a similar microvascular barrier known as "blood-spinal cord barrier (BSCB)". There are reasons to believe that the basic properties of the endothelial cells comprising the BBB or the BSCB are similar in nature (Sharma and Westman, 2002). Most of the neurochemical receptors identified in the brain endothelial cells so far have also been found to be present in the spinal cord endothelial cells (Stålberg et al., 1998; Sharma and Westman, 2002). Thus, the neurochemical mediators that are able to enhance the BBB permeability will also influence the BSCB permeability in a similar fashion.

Recently, it has been suggested that trauma induced release of glutamate will contribute to the membrane damage probably via formation of free radicals and nitric oxide (Lipton, 1996). Damage to the endothelial membrane will results in disruption of the BBB permeability and edema formation. However, apart from glutamate, several other neurochemical agents are also known to contribute to the secondary injury induced cell damage. These substances include serotonin, prostaglandin, dynorphin and many other neurotransmitters normally present in the CNS (Björklund et al., 1990; Nyberg et al., 1995). These compounds may be regarded as endogenous neurodestructive agents. It is believed that their interaction could also play important roles in the mechanisms of cell injury.

In addition to the above neurodestructive elements, a large number of other compounds are also released in the CNS following trauma. These substances include several kinds of immunomodulators, growth hormone and growth factors (Sharma and Westman, 1998; Stålberg et al., 1998). Most of these compounds act as endogenous neuroprotective agents. However, *in vivo* situation, a balance between the endogenous neurodestructive elements and the neuroprotective agents is crucial for the outcome following CNS injury, i.e., neuronal damage or cell survival. It is possible to alter this balance in favour of neuroprotection or neurodestruction by modifying the secondary injury

cascade using several pharmacological agents administered either before or after the primary insult. Thus, use of endogenous neuroprotective agents exogenously will enhance neuroprotection. Likewise, exogenous application of antibodies and/or antisense oligonucleotides directed against the endogenous neurodestructive elements will achieve neuroprotection.

Available evidences suggest that the mechanisms of cell injury either caused by trauma, ischemia, hypoxia, hyperthermia, stroke, infarction, irradiation or many other kinds of noxious insults to the CNS are quite similar in nature (Lipton, 1996; Sharma and Westman, 1998; Stålberg et al., 1998; Sharma and Westman, 2001). Thus, studies of neuroprotective agents in any model of CNS injury will provide novel information that can be used in a wide variety of neurological disorders to minimise cell injury. Keeping these views in consideration, an attempt has been made in this session to identify several neuroprotective agents that can reduce or thwart injury induced CNS damage in several experimental models.

Studies carried out by Cupello group using an *in vitro* model of hippocampal anoxia provide new information which suggests that creatine can be useful as a neuroprotective agent in brain ischemia. The authors (Paper I) clearly show that the cell damage caused by anoxia in the hippocampus is markedly reduced by creatine.

A possible neuroprotective effect of exogenously applied growth hormone on the trauma induced alteration in the BSCB permeability, edema formation and cell injury are examined by Nyberg and Sharma (paper II). Their results suggest that the growth hormone can be used as a neuroprotective agent following spinal cord trauma. This neuroprotective effect of growth hormone in the spinal cord seems to be mediated via IGF-1 receptors.

That the growth factor receptors influence cell injury in the CNS is further substantiated by the findings of Lafuente et al., (Paper III). The authors show that irradiation induced brain injury is associated with upregulation of vascular endothelial growth factor (VEGF) in and around the primary lesion. In addition, profound gliosis, edema and disruption of the BBB permeability can be seen around the lesion site. These new findings suggest that upregulation of VEGF reflects the endothelial cell injury and the BBB dysfunction plays an important role in trauma induced gliosis.

The works done in the laboratory of Alm (Paper IV) suggest that interaction between dynorphin and nitric oxide plays important roles in the molecular mechanisms of hyperthermia induced brain injury. Dynorphin is a well-known neurotoxic agent. However, its role in hyperthermia induced cell injury is not known. The authors (Paper IV) found an upregulation of dynorphin following hyperthermia in the brain regions exhibiting BBB dysfunction, edema formation and cell injury. Inhibition of nitric oxide synthase (NOS) by pharmacological agents in hyperthermia not only attenuated NOS upregulation and cell injury in the brain but also thwarted the increased dynorphin A immunoreactivity. These observations suggest that an interaction between dynorphin and nitric oxide plays important role in hyperthermia induced neurotoxicity.

The possibility that a balance between the excitatory amino acid glutamate and the inhibitory amino acid GABA in the spinal cord following trauma is crucial for cell injury is clearly demonstrated by Sharma and Sjöquist (Paper V). They found that a focal spinal cord injury was able to upregulate glutamate immunostaining in the adjacent spinal cord segment. In this region a marked downregulation of GABA immunoreactivity is apparent. Pretreatment with a new antioxidant compound H-290/51 that has a marked neuroprotective effect in the spinal cord following injury, significantly prevented the increase in glutamate immunoreactivity and arrested the decline of GABA immunoreaction in the cord. These results indicate that an interaction between glutamate and GABA plays significant role in spinal cord injury and antioxidant compounds can influence this balance.

The works reported by Winkler et al., (Paper VI) suggest that dynorphin is somehow involved in the pathophysiology of the spinal cord following trauma. This is meticulously shown by these authors using a topical application of the dynorphin A antiserum on the spinal cord before injury. This antiserum treatment not only attenuated cell injury, edema and breakdown of the BSCB, but was also able to reduce disturbances in the spinal cord evoked potentials (SCEP). These observations indicate that antiserum to dynorphin exerts powerful neuroprotective effects in the spinal cord at 5 h. However, this effect of the antiserum can be visualised much earlier using SCEP recordings.

Finally, Hernandez-Gómez et al., (Paper VII) examined the role of another important neuropeptide cholecystokinin (CCK) in an animal model of anxiety using a pharmacological approach. The authors found that the anxiogenic effects are mediated via CCK-B

receptors, however, the involvement of CCK-A receptors may not be ruled out. This observation provides a basis for further studies regarding the involvement of CCK in anxiety and stress disorders, the common phenomena leading to brain dysfunction.

We sincerely hope that further research using these new neuroprotective agents will explore their potential therapeutic values in the clinical setting in the near future.

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