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Chapter VII

Neurodegeneration and regeneration in the CNS. New roles of heat shock proteins, nitric oxide and carbon monoxide

Introduction

Our understanding on the molecular mechanisms of neurodegeneration or regeneration are not well understood. Neurodegeneration occurs in wide variety of CNS insults such as, trauma, ischemia, hypoxia, stroke, metabolic diseases and hyperthermia (Sharma and Westman, 1998; Stålberg et al., 1998). The CNS injury induces great suffering to the mankind and constitutes a heavy burden to the human society. Thus, new knowledge on the molecular mechanisms of neurodegeneration is highly needed to develop suitable therapy in order to minimise human sufferings all over the globe.

One way to treat the problems of neurodegeneration is to enhance the possibility of regeneration of specific CNS pathways or nerve connections and/or to restore the loss of neuronal functions by using several new class therapeutic agents or growth factors (Schwab and Bartholdi, 1996). Experimental evidences suggest that several neurotrophic factors enhance the neuronal sprouting and neural communication in the adult CNS following traumatic, ischemic or hypoxic insults. This indicates that growth factors and related compounds may emerge as potential therapeutic candidates to treat neural diseases in recent future.

In the CNS injury, no single chemical compound or factor is responsible for all the pathological mechanisms of the cell injury. Several endogenous neurodestructive as well as neuroprotective elements are released simultaneously during CNS insult and a balance between these factors determines the final outcome. There are reasons to believe that neuroprotective drugs or growth factors given as pretreatment or post treatment either enhance or potentiate the actions of endogenous neuroprotective compounds and/or inhibit or neutralise the effects of neurodestructive elements. Since, the basic mechanism of CNS injury occurring either following trauma, ischemia, hypoxia, or metabolic insults appears to be quite similar in nature, an increased understanding on the mechanisms of neurodegeneration or regeneration is of paramount importance to treat various CNS disorders in the coming future.

The CNS injury is associated with upregulation of heat shock protein (HSP) which are also referred to as "stress proteins". The functional significance of HSP induction in relation to cell injury is not yet clear (Lindquist, 1986; Sharma, 1999). It may be that induction of HSP represents

a protective phenomena of the CNS or it may simply reflects the magnitude and severity of the cell injury. The new results obtained by Westman et al., suggest that upregulation of HSP seen in hyperthermia mainly represents cell injury which seems to be mediated by oxidative stress. Pretreatment with antioxidants significantly attenuated HSP expression and cell injury supports this hypothesis.

The endogenous gaseous molecules, nitric oxide (NO) and carbon monoxide (CO) are known to modify neurochemical transmission and thus influence CNS function (Dawson and Snyder, 1994; Yamada et al., 1996). There are reports that NO and CO may somehow contribute to the CNS injury (Dawson and Snyder, 1994; Sharma, 1999). However, influence of growth factors on CO and NO function following CNS injury is still not well known. Using spinal cord injury as a model of neurodegeneration, Sharma et al., suggest that growth factors by attenuating cellular stress are capable of inhibiting NO and CO production in spinal trauma.

Oxidative stress as one of the important factor in contributing cell injury via production of free radicals is further supported by Alm et al., using the antioxidant compound H-290/51 in hyperthermic brain injury. The authors show that H-290/51 induced neuroprotection is related with its ability to attenuate NOS and HO-2 upregulation indicating that NO and CO are synergistically involved in hyperthermic brain damage.

However, apart from growth factors, Winkler et al. demonstrate that growth hormone can also be used as a new therapeutic agent to achieve neuroprotection following spinal cord injury. Using spinal cord evoked potentials as a principle tool to study pathophysiology of the spinal cord injuries, the authors show that the peptide can improve spinal cord conduction after trauma and offers significant neuroprotection.

Chronic neuropathic pain is well known to induce neurodegenerative changes in the spinal cord which seems to be mediated by several neurochemicals. The new results of Gordh et al., demonstrate that CO is involved in neurodegeneration caused by chronic neuropathic pain following spinal nerve lesion.

These observations open a new vista to understand the molecular mechanisms of neurodegeneration and to develop new therapeutic strategies to treat several kinds of CNS disorders in the near future.

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