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Neurobiology of the nitric oxide in the nervous system

Basic and clinical perspectives

Introduction

The recently identified gaseous molecule nitric oxide (NO) has influenced our basic concept of neurotransmission in the central nervous system (CNS). The NO is a free radical gas which does not require any synaptic machinery for storage or releases into the synaptic cleft for its action (Dawson and Snyder, 1994). NO diffuses quite rapidly among the cell membranes in order to induce its biological action. Since its half life is extremely short (about 5 sec) most studies in the CNS are concentrated to examine nitric oxide synthase (NOS), an enzyme which is responsible for its synthesis from the amino acid L-arginine (for review, see Dawson and Dawson, 1996). NOS exists in various isoforms and recently specific antibodies to these isoforms are available commercially which provide new tools in the NO research with great specificity and precision.

There are evidences that NO is involved in the control of blood flow, heart rate, blood pressure, long-term potentiation, depression and release of neurotransmitters (Schuman and Madison, 1994). Recently, NOS is found to be co-localised with several neuropeptides (Yamada et al., 1996) in various parts of the CNS which seems to be important in modulation of neurotransmission, activation of ion channels and/or modulation of receptor function and signal transduction mechanisms. There are indications that NO is involved in neurotoxicity in the CNS (Dawson and Dawson, 1996), however, this issue is still not well examined. Thus, it is still not clear whether upregulation of NOS and/or NO production seen in the CNS during various neurological diseases or in experimental models involving brain pathology such as, stroke, infarction, ischemia and trauma is contributing to cell injury (Dawson and Snyder, 1994; Schuman and Madison, 1994; Dawson and Dawson, 1996).

Experiments based on neuronal NOS null mice provides one of the most strong evidence supporting the role of NO in neurotoxicity in ischemia (Dawson and Dawson, 1996). Thus, the NOS null mice are quite resistant to ischemia induced cell damage in the brain. On the other hand, use of NOS inhibitors in ischemia, stroke or infarction provide contradictory results. Thus, the hypothesis that NO is involved in cell injury and cell death is still controversial. There are indications that blockade of endothelial isoform of NOS (eNOS) aggravates ischemic injury. Whereas, blockade of neuronal NOS (nNOS) in pathological conditions is beneficial for cell survival (see Dawson and Dawson, 1996). Thus, it seems quite likely that specific inhibi-

tors of various isoforms of NOS are crucial in maintaining cell injury or cell survival, a feature which require additional investigation.

This section is focused on some new physiological and pathophysiological aspects of NO in the CNS. The emerging role of NO in thermoregulation is dealt by Simon in experimental models using a new approach. It appears that NO seems to be involved in the mechanisms of thermoregulation and hyperthermic mechanisms of brain injury as well. Alm et al., provide a direct evidence that increased nNOS in the CNS is harmful in hyperthermic brain injury. This is meticulously shown by use of a new antioxidant compound H-290/51 which prevents both NOS upregulation and cell injury suggesting that NO production from activated NOS is harmful.

The role of NO in pain and other behaviour has been speculated earlier. However a clear role of NO in chronic pain mechanisms is uncertain and treatment of chronic pain and/or neuropathic pain is still a challenge to many clinicians world-wide. In order to search some new strategies to treat this disorder, Gordh et al., have some idea about how L-NAME can influence NOS upregulation in a rat model of chronic neuropathic pain in relation to morphological alterations in the spinal cord.

The physiological aspect of water intake and its control in neurons in subfornical organs is a new concepts and Schmid examines the involvement of NO in this phenomena which appears to be mediated via cGMP related mechanisms.

Trauma to the spinal cord is one of the important cause of disability in human population and no success to treat this medical catastrophe has yet been achieved. Paralysis, paraplegia and life-time rehabilitation are the main problems of spinal cord injury victims throughout the world. Thus further research in this field is highly needed. It appears that NO is involved in ischemia, stroke and infarction, however a role of this gaseous molecule in spinal cord trauma is not yet fully established (Sharma et al., 1996). It seems quite likely that the basic mechanisms of cell injury following trauma, ischemia, infarction or stroke are quite similar in nature, thus it would not be surprising that NO can also influence the pathological mechanisms of spinal cord injury. Thus based on new knowledge of cell injury further therapeutic strategy seems to be worthy of investigation in CNS trauma.

In this regard, in our laboratory (Sharma et al.), we used local application of NOS antiserum on the traumatised spinal cord and examined the pathophysiology of cell injury in a rat model. The results of NOS antiserum are compared with standard NOS inhibitors in relation to NOS immunohistochemistry. Our results show that application of NOS antiserum is capable of attenuating NOS upregulation and thereby induces some neuroprotection. Another way to approach this problem is to examine spinal cord conduction following injury in relation to NOS upregulation and its modification with pharmacological agents known to influence secondary injury mechanisms. Winkler et al., analysed the spinal cord evoked potentials (SCEP) in traumatic injury and examined upregulation of NOS in order to see whether pretreatment of drugs can influence either NOS or SCEP activity following trauma in relation to cell injury in the cord.

The other important aspect following spinal cord injury is to reduce paraplegia or paralysis and is to enhance axonal regeneration in the spinal cord following trauma. Regeneration and repair mechanisms are the other most important aspect of spinal cord trauma which may have great potential in future therapy for spinal cord injury victims. However, our present knowledge regarding the involvement of NO in regeneration and repair mechanisms following trauma is still very rudimentary. To address this question, our group (Sharma et al.) examined the potential efficacy of BDNF and IGF-1 in attenuating NO production and cell damage in spinal cord injury. It appears that the neuroprotective effects of BDNF and IGF-1 are somehow related with their ability to downregulate NO activity as evident with a reduced NOS expression in the spinal cord following trauma.

These new results provide support for an important role of NO in the pathophysiology of the CNS. Further studies in this direction will expand our knowledge regarding the role of NO in various diseases processes afflicting CNS.

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